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ABSTRACT

This booklet is concerned with the area of clinical depression. Questions about clinical depression are briefly answered in an overview section and are examined in greater detail in the five chapters that follow. In chapter 1, depression is defined and various types of depression are identified. The origins of depression are explored in the second chapter and factors such as sex, age, and other demographic variables are discussed. The role of genetic transmission in clinical depression is examined, and the functions of the brain and neuroendocrine system in clinical depression are explained. Other factors contributing to depression are described: psychophysiology, health and physical illness, personality, cognition, behavior, and life events. The third chapter looks at depression in children and in the elderly and the fourth chapter examines the relationship between depression and suicide. Treatment alternatives are discussed in the fifth chapter, including psychotherapies (cognitive/behavioral therapy, behavior therapy, psychodynamic psychotherapy); pharmacotherapy (tricyclic antidepressants, monoamine oxidase inhibitors, lithium); and electroconvulsive treatment. Current National Institute of Mental Health research programs are listed and briefly described in the conclusion and a table is included which offers suggestions for when and where to seek help. (NRB)

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WHAT WE KNOW

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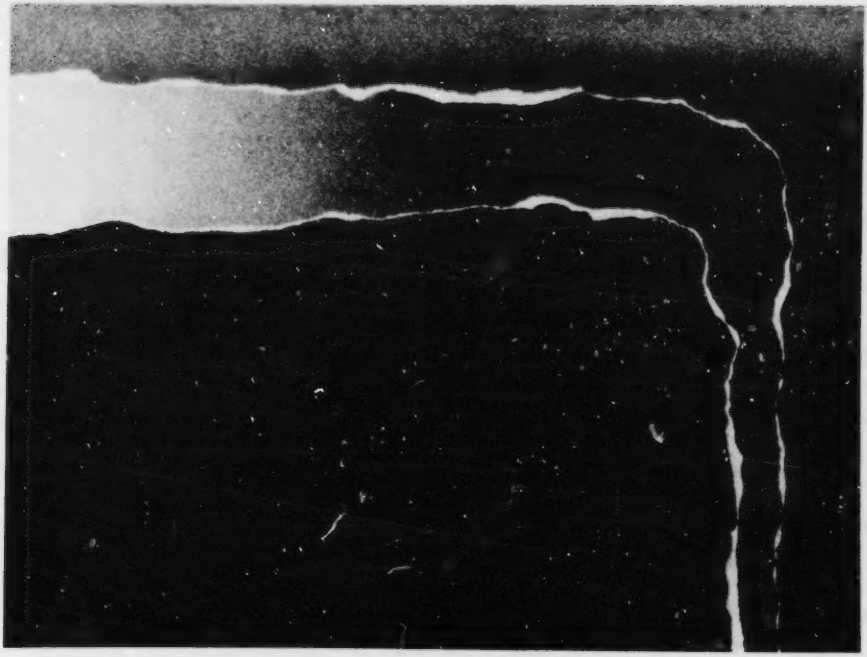
DEPRESSION
WHAT WE KNOW



Brana Lobel, Science Writer
and
Robert M.A. Hirschfeld, M.D.
Chief, Center for Studies of Affective Disorders
Division of Extramural Research Programs
National Institute of Mental Health

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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National Institute of Mental Health
5600 Fishers Lane
Rockville, Maryland 20857

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Foreword

In reply to a letter requesting information on depression in May 1982, newspaper columnist, Ann Landers, told her readers that a pamphlet was available from the National Institute of Mental Health. That column inspired thousands of other readers to write directly to the Institute asking for information on depression. In January 1983, Dr. Herbert Pardes, then NIMH director, wrote to Ann Landers informing her of the sizable public response to her May column. Ms. Landers printed that letter. Both letters brought over 150,000 inquiries to the Institute seeking information about depression. They told heart-rending stories of tremendous suffering among individuals and their families afflicted with depression.

The purpose of this booklet is to provide people with an understanding of our knowledge on the causes of depression and its various treatments. A quick reading will reveal that there are a wide range of very effective treatments for depression, but that the vast majority of people who suffer from depression do not receive them. Most people either fail to recognize that they are suffering from depression or, even when they do recognize it, they often receive inadequate or even improper treatment.

Cost estimates of the effects of depression are staggering. Not only does depression account for a sizable portion of mental illness in America, but a large portion of drug abuse and alcoholism related to depression. Costs include treatment of the illness, lowered work productivity, job absenteeism, or even permanent disability.

NIMH has a long-term commitment to research on the causes and treatment of depressive disorders. The Institute sponsors conferences and publications for exchange of information among depression researchers and clinicians in various disciplines. NIMH has also developed and supported large collaborative clinical research programs related to depression which offer promise of more effective solutions to this serious public health problem in the future.

Larry B. Silver, M.D.

Acting Director

National Institute of Mental Health

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Overview

Depression. Almost everyone knows what the word means. Or do they? In fact, the word "depression" has many different meanings. In psychiatry, depression may range from a transient, momentary feeling of emotional dejection all the way to a severe disorder that can stop a person from functioning, cause a slowdown of body processes, and even, in some cases, lead to death.

The subject of this booklet is clinical depression, or the clinical depressive syndromes. These are a group of treatable disorders that have been identified by mental health researchers and clinicians. Clinical depression is a complex subject; a great deal still remains to be learned about it, but much is known already. Following are ten of the most common questions asked about clinical depression. This overview section offers brief answers to these questions; the rest of the booklet provides more extensive information.

- What is clinical depression?
- Who gets depressed?
- Can depression be treated?
- Will the depressed person recover?
- Will the depression return?
- How likely is the possibility of suicide?
- What causes depression?
- Does depression run in families?
- Can depression be prevented?
- Where can the depressed person go for help?

What is clinical depression?

The blues. The blahs. The pits. Down in the dumps. Under the weather. Lower than a snake's belly. Just about everybody has a favorite phrase to describe a depressed mood. In some ways, the condition is almost like an object: we know its location is "down," and its color is blue, gray, black, or sometimes no color at all. But for the most part, people regard depression as a feeling, a mood, an emotion. As such, depression is a normal human experience; an unavoidable

part of existence. Sadness, grief, frustration and discouragement are the dark threads interwoven in life.

The question becomes: when does depression cease to be a normal condition and become an abnormal clinical state? In some cases, the boundaries are unclear, but increasingly, researchers and clinicians view a combination of intensity, severity, and duration of depressive symptoms as the benchmark for clinical depression. Characteristically, the onset of clinical depression is signaled by a depressed mood and/or loss of interest in usual activities. Symptoms may include appetite, weight and sleep disturbances, hyperactivity or lethargy, anxiety, crying, slowed thinking, suicidal tendencies, and feelings of guilt, worthlessness and hopelessness. When these symptoms persist more than two weeks, a clinical depression may be occurring. Depression can be associated with another psychiatric disorder such as schizophrenia or alcoholism, or of a physical illness, for instance, a viral disease or an endocrine disorder. However, clinical depressions often exist without any other intermediary disturbance. It is these conditions, the clinical depressive syndromes, which include unipolar and bipolar disorders (the latter also known as manic-depressive illness), and cyclothymic and dysthymic disorders (the latter also known as depressive neurosis) that are the major focus of current research and clinical attention and the subject of this booklet.

Who gets depressed?

Depression afflicts all types of people: rich and poor, old and young, the college professor and the ditch-digger. Back to the beginning of recorded history and literature, instances of depression have been described. In the Old Testament, both King Saul and Job, from descriptions of their behavior, suffered from serious depressions. Shakespeare, too, describes instances of depression. Hamlet, the "melancholy Dane," is probably the prime example. His soliloquy on suicide, "To be or not to be," is one of the best-known pieces of poetry in the English language. Novelists, poets, and dramatists throughout Western history have depicted depression: Poe, Dostoevski, Hawthorne; Milton and Blake; Ibsen and Eugene O'Neill. The famous and powerful, no less than the ordinary and obscure have endured it. Abraham Lincoln was a sufferer; Winston Churchill as well, who termed his periodic depression, with chilling accuracy, "the black dog." The actress Vivien Leigh, the Broadway producer Joshua Logan, responsible for such hit plays as *South Pacific*, and the author Leo Tolstoy suffered some variant of the illness. More recently, Senator Thomas Eagleton and the astronaut Edwin (Buzz) Aldren are examples that come to mind.

For some time it had been thought that depression was more common to late-middle and old age, but more recent surveys indicate that a higher proportion of younger persons are depressed, that depression

seems to occur as much or more in the 20–40 age range as in older persons, and that even depression in infants, children, and adolescents has been under-identified. In general, clinical depression is twice as common in women as in men. Possible reasons for this are genetic, sociocultural, hormonal, diagnostic practices, and women seeking help more often than men. All of these possibilities are receiving a great deal of research attention.

From 4 to 10 percent of the American public now suffers from an identifiable depressive disorder. Over the course of a lifetime, perhaps 25 percent of the population will experience a major depressive episode. In fact, clinical depression is so prevalent in the United States that most people have a friend or relative who has suffered or is suffering some variant of the disorder.

Can depression be treated?

There are a number of effective treatments available for clinical depressions; these include several specific forms of psychotherapy, a variety of antidepressant drugs and lithium, combinations of drugs and psychotherapy, and electroconvulsive treatment (ECT). The preferred treatment depends in part on the type and severity of the depression, and in part on other factors such as the physical condition and age of the depressed person. Many people are helped by treatment, although all treatments do not work equally well for all people. Some people with recurrent unipolar or bipolar disorders have been helped substantially by long-term maintenance treatment.

Will the depressed person recover?

With adequate treatment, improvement should occur in about one month for most depressions.

Most serious depressive episodes are self-limiting, and, untreated, last for an average of about a year or more. Untreated episodes of mania and depression in bipolar disorder are likely to be of shorter duration: several days or weeks to a few months. Most people return to their normal level of functioning after the episode, although for 20 to 35 percent of the cases the disorder is chronic, causing considerable symptomatic and social impairment. Milder forms of clinical depression, i.e., cyclothymic and dysthymic disorders, untreated, are considered chronic. But it should be remembered that every person is different and reacts differently to treatment.

Will the depression return?

Approximately 50 percent of people who have had a major clinical depressive episode will never have another one. For the remaining 50 percent, the course is variable: there may be a few episodes with

intervals of many years of normal functioning, episodes may be more frequent, or may cluster. For some, the frequency of episodes will increase with advancing age. Most individuals who have one or more manic episodes will eventually also have a depressive episode. For these individuals, the course is similarly variable. *Adequate treatment can minimize or reduce the severity of the episode in many cases.*

How likely is the possibility of suicide?

Long-term followup studies of persons with serious clinical depressions not associated with other psychiatric disorders have found a suicide rate of 15 percent. A greater percentage of women attempt suicide, but a greater percentage of men successfully complete the act. The depressed individual considered an especially high suicide risk is a white man over the age of 45 who is separated, widowed or divorced, lives alone, and is unemployed or retired. A number of researchers have found that the likelihood of completed suicide in depressed people is related to hopelessness and negative expectations about the future, rather than to other symptoms. With treatment, these feelings can often be overcome.

What causes depression?

There seems to be no single cause for clinical depressions. Rather, there are a variety of factors, some of which may have more weight in certain types of depressions than others. Among these factors are genetic predisposition, biological imbalances or abnormalities, personality characteristics, learned behavior and thought patterns, stressful life events, social and economic class, culture, age, and sex.

Does depression run in families?

There is strong evidence that a tendency toward both bipolar and some forms of nonbipolar disorders runs in families, and likely has a genetic component. There is also speculation that learned behavior or persistent environmental conditions in some families may lead to clinical depression in successive generations.

Can depression be prevented?

In general, the onset of a clinical depression cannot be prevented. The condition can, however, be identified in its early stages and treated, and for those with recurrences, these can sometimes be prevented or the severity of the episodes markedly reduced. Young people at high risk for clinical depression because of family history of first degree relatives (parent and/or siblings) with the disorder may be

identified and treated early in their lives to prevent the recurrence of full-blown episodes.

Where can the depressed person go for help?

The first line of diagnosis and treatment is often the family doctor or local clinic, where symptoms of depression can be evaluated to rule out the possibility of a physical illness. Clinical depressive syndromes may require treatment by a qualified mental health professional. While treatment is often on an outpatient basis, sometimes inpatient treatment is necessary. For a more complete listing of sources of help, see table 2 on page 65.

Chapter 1

What Is Depression?

Types of Depression

What distinguishes ordinary sadness, or feeling "down," from clinical depression? This question continues to concern clinicians and researchers. Some depressive conditions are clearly definable, while other states overlap in some ways with normal functioning.

The term "depression" has many meanings: a mood, a symptom, and a group of syndromes. The mood, feeling, state, or emotion is what many people think of when they use the word "depression." It is a pervasive feature of ordinary human experience: at various times, sadness, disappointment, frustration, discouragement, and allied states are unavoidable aspects of life.

Depression can also be a symptom of a physical or psychiatric illness or other clinical condition. As a symptom, it can be associated with a number of psychiatric disorders, including schizophrenia, anxiety, neurosis, alcoholism, hysteria, and personality disorders. It is also associated with a variety of physical illnesses including disorders of the endocrine system and the central nervous system, viral diseases, and responses to certain drugs.

The clinical depressive syndromes are what mental health researchers mean when they speak of "clinical depression."* This is a group of increasingly identifiable subtypes of depression based on specific sets of symptoms and associated factors. The current benchmark for clinical depression, compared to normal depressed mood, depends on the intensity, severity, and duration of symptoms. Generally (except in the case of bereavement over the death of a loved one), if the depressed mood and associated symptoms last for more than 2 weeks, and if they are of sufficient intensity to interfere with ordinary daily activities, this is considered a clinical depressive syndrome.

*The terms "depression" and "clinical depression" are used synonymously.

In 1980, the American Psychiatric Association published the third edition of its *Diagnostic and Statistical Manual* (the DSM III). In this book, experts in the field have defined clinical depressive syndromes in a way that is useful both to clinicians and researchers. The classification of the various types of depression, also called affective disorders, are shown graphically in figure 1. Following are the most common types of clinical depressions described in the manual.

Major Depression

This condition is characterized by a depressed mood, which can run from a feeling of dullness or apathy all the way to total hopelessness and deep despair. It is often accompanied by frequent crying. Anxiety is sometimes present: the person may be tense, nervous and jittery or sad and miserable. Irritability, touchiness and anger can occur. Changes in thinking also characterize this condition: slowing-down of thought, inability to concentrate, difficulty with memory, indecision. Often the person believes himself or herself to be helpless, worthless, guilty. Self-blame, lowered self-esteem, and feelings of failure are common; thoughts of suicide and sometimes active plans are not uncommon.

There is usually a series of changes in somatic or body functioning. Sleep disturbances are common: there may be difficulty getting to sleep, troubled sleep with frequent wakings, or early awakening (2 or 3 hours before the usual time) with inability to go back to sleep again. For some, the problem is oversleeping. Eating problems may occur: the most characteristic pattern is loss of appetite and weight, but increased appetite and weight sometimes also occur. Energy loss, feelings of lethargy or inertia, and slowed speech and movement may also occur, although sometimes the reverse may be true and there is agitation and hyperactivity (restlessness and pacing, for instance). Other physical changes, such as alterations in bowel habits (constipation is common), dry mouth, headaches, and a variety of aches and pains are sometimes seen.

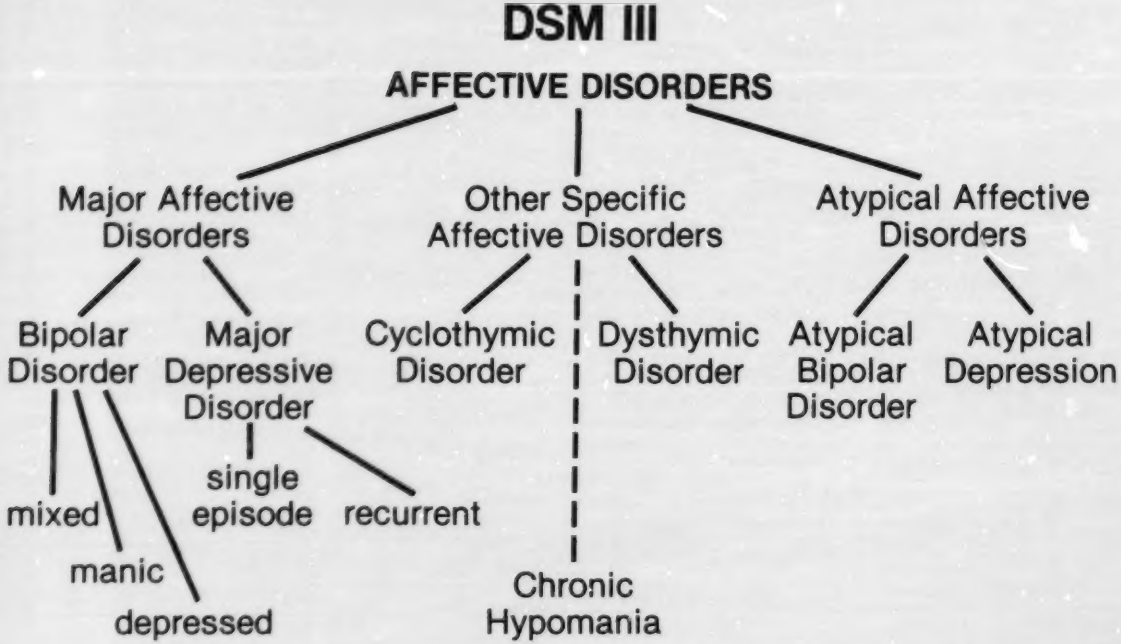
Perhaps most characteristic in depression are the general changes in behavior: there is a loss of interest in things, people, events and activities previously considered pleasurable, a diminished capacity for affection, a loss of interest in sex, and an overall loss of satisfaction with life.

In major depression, these symptoms are marked; they range from moderate to severe and seriously interfere with, or actually prevent a person from leading his or her usual life. In some cases, the condition is accompanied by psychotic symptoms, such as delusions and hallucinations.

Unipolar and Single-Episode Depressive Disorder

Approximately 50 percent of people who experience a major

Figure 1


DSM III
AFFECTIVE DISORDERS
Major Affective Disorders
Other Specific Affective Disorders
Atypical Affective Disorders
Bipolar Disorder
Major Depressive Disorder
Cyclothymic Disorder
Dysthymic Disorder
Atypical Bipolar Disorder
Atypical Depression
mixed
manic
depressed
single episode
recurrent
Chronic Hypomania

depression have only one serious episode in their lifetimes. For the others, the condition reappears and is called *unipolar disorder* (meaning recurrent major depressive episodes). The course of unipolar disorder may vary: episodes may be separated by long intervals, sometimes many years, of normal functioning, they may be closer together, or may cluster. For some, episodes increase in frequency with advancing age. Symptoms of a major depressive episode usually appear over a period of days to weeks, although sometimes they are more sudden. Untreated, an episode generally lasts an average of 1 year.

Manic Episode

In this condition, the mood is elevated and euphoric (the so-called "high"). Irritability may also be present. People in a manic state are hyperactive, and often get by on very little sleep. They have inflated or grandiose ideas about themselves. Their speech can be pressured and rapid, their thoughts move very quickly from one topic to another, and they are easily distractable. They often show very poor judgment and may go on wild spending sprees, invest unwisely in business, or have indiscreet sexual relationships. Energy and sociability are increased. There are sometimes psychotic symptoms such as hallucinations and delusions. The latter are often of a grandiose variety — for example when the depressed person claims a special relationship with a celebrity or well-known political figure. The symptoms can range from moderate to severe; with moderate symptoms, a stranger may not recognize the condition as a disorder, but those who are close to the individual may see the behavior as excessive and unusual. Manic episodes usually begin suddenly, and symptoms increase over a few days. They can last for a few days to a few months; typically they are much briefer than depressive episodes (see figure 1).

Bipolar Disorder

Bipolar disorder (sometimes called manic-depressive illness) is characterized by episodes of mania alternating with episodes of depression. In bipolar disorder the first episode is often manic; although a very small number of people have only manic episodes, most people will have both manic and depressed episodes. Frequently an episode of one type is followed immediately by a brief episode of the other type. In general, the episodes are more frequent and shorter than those in unipolar disorder. The course over a lifetime, as with unipolar disorder, is variable.

Dysthymic Disorder

This condition is also called "depressive neurosis." It is characterized by depressed mood (dysphoria) or loss of interest in usual

pleasures and activities, accompanied by the associated symptoms of unipolar disorder but without the severity or duration found in the latter. The condition may persist, or it may be intermittent, with "normal" moods that last from a few days to a few weeks. For adults, the condition must have been present for 2 years to be diagnosed as a clinical depressive syndrome. Psychotic symptoms are not present. Dysthymic disorder can be described as mild to moderate; onset is unclear and the course is chronic.

Cyclothymic Disorder

This condition is characterized by a chronic mood disturbance of at least 2 years' duration, involving numerous periods of depression and hypomania (mild manic symptoms). Associated symptoms will be neither as severe nor as long-lasting as in a serious manic or depressive episode. In cyclothymic disorder, the depressive and hypomanic periods may be separated by periods of normal mood lasting for months at a time; or the two types of periods may be almost simultaneous or may alternate with each other.

Depressed and hypomanic periods are characterized by "paired symptoms." For instance, feelings of inadequacy during depressed periods and inflated self-esteem during manic periods; social withdrawal and uninhibited quest for companionship; sleeping too much and decreased need for sleep. There are no psychotic symptoms; onset is usually unclear and the disorder has a chronic course.

Social and Emotional Costs of Depression

Like a stone dropped into a pond, the impact of clinical depression spreads to encompass a far wider area than just the individual involved. "No man is an iland, entire of itselfe; every man is a peece of the continent, a part of the main;" the poet John Donne observed over 400 years ago. This is as true in the 20th century as it was in the 16th. The effects of depression are truly far-reaching; they spread not only concentrically around the depressed person into his or her environment, but can also influence future generations.

Estimates have been made of the economic costs of mental illness, drug abuse, and alcoholism in the United States. These figures are not specific for clinical depression. However, current knowledge suggests that not only does depression account for a sizable portion of mental illness in this country, but, in addition, a fair percentage of drug abuse and alcoholism are caused by or related to depression. In a study done for the Alcohol, Drug Abuse and Mental Health Administration (ADAMHA), the total cost of these three conditions to America in 1977 was conservatively estimated at $106 billion. To put this figure into perspective, it is close to one-sixth of the total budget for the United States Government in 1983 ($718 billion).

Whatever percentage of these costs is caused by clinical depression

it is a large one. Costs include not only treatment of the illness, but also losses connected with lowered productivity, job absenteeism, and permanent withdrawal from the work force because of illness or death. In an economic context, productive members of society include not only the man or woman who works at a job paid in dollars, but also the housewife, whose value must be calculated in terms of services. The business or company that pays to provide treatment for employees also feels the impact of clinical depression. More difficult to calculate are the present and future losses incurred by depressed youth; school problems that lead to alterations in career and job choices are one example.

Social costs are not measurable in dollars. Clinical depression can lead to a host of related problems: on the emotional level, grief and pain; on the social level, family conflict, antisocial behavior, physical illness, and death. No one has yet been able to come close to providing a measurement for these complex chains of cause and effect, although researchers are attempting to do so. Some are observing the effects of clinically depressed parents on their children; others study divorce in depressed as compared to nondepressed populations. But even these more specific areas of research cannot capture the complexity of the difficulties in an individual's life as the result of a clinical depressive episode or a series of these: love lost, relationships ended, potentials never developed, roads not taken. Multiplied by millions, the cumulative result of these individual disruptions is indeed beyond measurement.

Classifying Depression

In the search to understand and treat clinical depression, observing symptoms and obtaining the individual's history is only the beginning. The ultimate goal is to identify the causes of clinical depression, which researchers now think represents a number of conditions with somewhat similar manifestations.

One of the main problems with research in the past arose from disagreement on basic classification issues. Researchers and clinicians have used a number of different systems and typologies for clinical depression, including ones based on observation, inference, theory, and the classical medical model of disease. The range of different systems used to classify depressed subjects limited the utility of much research; in addition to questions as to whether the "types" were valid, research findings were difficult and sometimes impossible to compare and correlate with each other. In 1970, the National Institute of Mental Health (NIMH) established the Collaborative Program on the Psychobiology of Depression within its Clinical Research Branch. The object of this program was to organize and stimulate the research effort into the nature and causes of clinical depression; a major concern was the refinement of existing systems of classification.

Researchers are moving toward a common terminology; however, in a subject as complex as clinical depression, a great deal still remains to be learned. Many terms and distinctions used in the past are still useful in identifying certain characteristics of clinical depression; they may strongly correlate with subtypes, aid in observation, or give clues about causality. A few of the more common distinctions are described below.

Psychotic/neurotic

In early research on depression, a distinction was made between clinically depressed people who were psychotic and those who were depressed without being psychotic. Some researchers considered psychotic depression a specific condition of organic origin, as contrasted to "neurotic" depression which was milder and thought to be largely of environmental origin. Other theorists considered that psychotic and neurotic depression were not two separate conditions, but two different ends of a single continuum. Currently, neither of these theories has been proven. One difficulty with this distinction is the multiple meanings given to both psychotic and neurotic depression. The term "psychotic depression" may refer to severity, to psychotic symptoms such as delusions and hallucinations, to severe social incapacitation, and/or to somatic symptoms. The term "neurotic depression" may be used to mean the absence of any or all the major characteristics of psychosis, or to depression stemming from "neurotic conflicts" as proposed by psychoanalytic theory.

Endogenous/nonendogenous

The concept of endogeneity in clinical depression has been used over time in a number of different ways. "Endogenous" means "coming from within." Currently, the term "endogenous depression" refers to a set of symptoms involving early morning awakening, loss of appetite and weight, disturbances of the psychomotor system such as agitation and lethargy, daily variations in mood (often, more noticeable depression in the morning), severe depressed mood, and lack of reaction to environmental stimulation. Many of these symptoms involve disturbance of basic bodily functions; the endogenous condition is suspected of having more direct relationship to biological factors than some other types of depression. Recent research has shown that people characterized as endogenously depressed tend to be older and more severely ill than other depressed people, have basically normal personalities before the depressive episode, and show the greatest response to antidepressant drug treatment.

Primary/secondary

Clinical depressions can be classified as primary: that is, the

depressed person has had no previous psychiatric disorder (or has only had episodes of depression or mania), or secondary: the depressed person has a pre-existing psychiatric disorder (for example, schizophrenia or alcoholism) on which a clinical depression is superimposed. This is primarily a research distinction intended to select a group of "pure" depressive subjects for a better study of causes.

The primary/secondary distinction is also used in connection with physical illness. People who develop depressions clearly caused by or associated with certain diseases, drug responses, or other physical conditions are considered to have secondary depressions.

Unipolar/bipolar

Unipolar disorder is defined as one depressive episode or a history of only depressive episodes, or far more rarely, one manic episode or a history of only manic episodes. Bipolar disorder, in contrast, is the occurrence of both manic and depressive episodes, either separately or concurrently. There is increasing evidence that unipolar disorders and bipolar disorders represent different types of depression, with some overlap. Much information from genetic, biochemical, and pharmacological studies supports this distinction.

All of the diagnostic/typological approaches described above are *categorical*, that is, they consider the depressive syndrome as a discrete condition, separate from other psychiatric conditions. An analogy in physical medicine would be pneumococcal pneumonia. Critics of categorical approaches suggest that patterns of characteristics in clinical depressions have not yet been well enough identified to justify such typologies, that they require unnecessary narrowing of focus, and that they tend to focus exclusively on symptoms and disregard other variables. As an alternative, a *multiaxial* system has been proposed, and is currently considered the most promising way of classifying clinical depressions. The five major axes, or factors considered, are symptoms, circumstances associated with symptoms, previous duration and course of symptoms, quality of personal relationships, and level of work functions. A multiaxial approach has been introduced into the current U.S. psychiatric diagnostic manual, the DSM III, which is widely used by American researchers and clinicians. Prior editions of the DSM (I and II) were based upon a totally categorical system.

There has been a tendency for researchers to type according to the predominance of either biological or psychological features. While the study of distinct "types" of depression is useful for research purposes, it seems clear to researchers and clinicians that there are large numbers of depressed people who do not show a preponderance of either set of characteristics, but are "mixed." Further research must seek a bridge across the two sets of factors which will allow for a more comprehensive and meaningful approach to classification.

NIMH has sponsored development of two research tools to assist in developing a valid and standardized classification system. They are the *Schedule for Affective Disorders and Schizophrenia* (SADS) and the *Research Diagnostic Criteria* (RDC). The SADS is a comprehensive, standardized recording guide and interview form. The RDC is a set of operational diagnostic criteria that span current systems of classification. The RDC is particularly useful in establishing the validity of subtypes, because its broadness does not prematurely rule out overlapping categories. The RDC categories have high reliability and are currently being widely used in depression research to study questions relating to treatment outcome, epidemiology, genetics, and biology.

If this tour through the intricacies of classification has been somewhat confusing, a clarifying analogy may be apt. Some fish are better caught with a rod, others with a net. Current research in depression indicates that a well-woven net to catch many fish is the best approach. The SADS, the RDC, and the DSM-III are nets of this sort, and a promising catch is beginning to be hauled up. A great deal of the confusion and error in diagnosis is being eliminated, and further refinement in addressing the ultimate question, that of causes, is being made possible.

Chapter 2

The Origins of Depression

Why do people become clinically depressed? Why do some people become depressed while others do not? Why do women seem more vulnerable to depression than men? What is the relationship of alcoholism to depression? Is depression "in the genes," or do we learn it? These are the kinds of questions people are asking and depression researchers are attempting to answer.

In the historical past, clinical depression was called *melancholia*, and was thought to have a single cause. The ancient Greeks thought that the body produced four "humors," fluids that influenced temperament and behavior, and that an excess of one, black bile, would create melancholia. (Melancholia means "black bile" in Greek.) In the Middle Ages, melancholia was seen predominantly as a religious problem, often the result of demonic possession. In the 19th century, the psychiatrist Kraepelin viewed recurrent clinical depression as hereditary. Researchers are now convinced that there is no one cause; there are many, and a number of approaches must be used to investigate causes. Thus, depression investigators now use a "multifactorial model," that is, they look for the interaction of several factors that influence the occurrence of clinical depression.

What Causes Depression?

The current search for causes is complex; research investigations are often limited to a specific area. Examples include epidemiological studies, which examine age, sex, social class and other variables in large groups of people; biological studies, which include the examination of brain functioning and the endocrine system, as well as the observation of sleep patterns, biorhythms and cycles of bodily activity; physical illness and nutrition; genetics; the physiological effect of drugs; the psychologies of learning and of personality; and the examination of the effect of stress and life events.

Current researchers in depression seem to resemble the blind men

examining the elephant: the biologist may have hold of the tail, the social researcher may have grabbed the ear, the psychological theoretician embraced the foot, but how these parts fit together is still unclear. And, to carry the analogy even further, researchers suspect that as the parts connect, they will discover not just one elephant, but a whole herd: different sizes, shapes, behaviors. Not only are there many causes for clinical depression that interact in different ways for different people, but there are a number of different "depressions," not merely one kind. Researchers must not only separate possible causal factors and study them individually, but must also connect and synthesize them into larger groupings. No one condition, event, or factor is absolutely responsible for clinical depression; instead, a number of influences converge along what has been called a "common pathway" that produces the depressive syndrome.

Epidemiology

Epidemiology, the large-scale study of population groups, is an important aid in investigating the causes of clinical depression. In the United States, the study of the epidemiology of mental disorders began in the 19th century, but it was not until the early 1970s that standardized diagnostic categories began to be used by American epidemiologists. With the increasing use of these categories, further refinements have been made in the study of depressed people and control groups on the basis of age, sex, and other variables. Recently, researchers in depression have concentrated on three broad categories: bipolar disorder, non-bipolar depression (a category which includes all other identified clinical depressive syndromes), and depressive symptoms (a category of less severity, often determined by self-report questionnaires rather than clinical observation; in general, people in this category do not meet the criteria for clinical depression, but there is some overlap). Terms commonly used in epidemiology are *incidence*: the number of new cases of a disorder occurring in a given time period, and *prevalence*: the number of people who have the disorder at a given point or over a given period of time.

The concept of *risk factor* is a particularly important one for epidemiology. A risk factor is a condition which increases the likelihood of a person developing a particular disorder. Since current findings have shown that women are twice as likely to develop major depressions as men, being a woman is a risk factor for major depression. The "risk factor profiles" for those with depressive symptoms and those with non-bipolar clinical depression are similar, and differ from the profile for those with bipolar disorder. Those at risk for depressive symptoms and non-bipolar clinical depression include women, the young, the lower classes, the unmarried and unattached, and those who have recently experienced an interpersonal loss. In bipolar disorder, although life events such as interpersonal loss may

play a similar role in onset, neither being female nor unmarried poses an increased risk for the disorder. However, bipolar disorders may show a greater prevalence in the higher social classes.

The findings outlined below represent what is known at the present time, but cannot be taken as definitive. Many important areas of investigation have received relatively little research attention to date. Some existing findings may be questionable because of variations in diagnosis. Scientists are devoting a great deal of effort to further refining and standardizing epidemiological findings connected with depression.

One important new investigation is the Epidemiological Catchment Area (ECA) Program, a series of studies performed by independent research teams in collaboration with the NIMH Division of Biometry and Epidemiology. Target areas are in five states: Connecticut, Maryland, Missouri, North Carolina, and California. At each site, interviews are being conducted with 3,000 community residents and 500 institutional residents (those in mental hospitals, prisons and nursing homes), in order to study specific mental disorders, including clinical depression, in these population groups. The ECA study will also provide a test of the validity of the NIMH Diagnostic Interview Schedule (DIS), a recently developed research tool that combines current diagnostic concepts and survey techniques. It is hoped that the ECA study will be able to provide an accurate assessment of the incidence and prevalence of specific mental disorders in the United States. The very large target population of this study increases the probability that the data produced will be reliable.

Sex

The preponderance of studies in many countries indicates that women have more depressive symptoms and more non-bipolar clinical depression than men at a 2:1 ratio. The exception to this is bipolar disorder, for which the prevalence rates in men and women are approximately equal.

Researchers currently agree that this 2:1 ratio represents a real figure, and not an artifact created by the fact that more women tend to seek medical and mental health services than men. Women also describe depressive symptoms in community surveys more often than men do. A consideration that might influence this is that women may express their complaints more freely than men.

Theories about female hormonal and endocrine system involvement have been advanced to explain the preponderance of depression in women. Hormones do affect mood, but current evidence cannot explain the magnitude of the difference of prevalence in women as compared to men. While the postpartum period does increase the risk for clinical depression in women, specific causes for this are not yet understood. Similarly, depressive reactions to oral contraceptives

and premenstrual distress are still under investigation. Recent research has shown that menopause does not predispose women to clinical depression, that depression among women does not rise in the menopausal years, and that in fact the condition previously called "involutional melancholia," or postmenopausal depression, does not exist as a separate entity.

Early genetic theories had suggested X-chromosome-linked transmission of depression, which, if by a single dominant gene, would affect more women than men. However, these have been rejected by researchers as not being borne out in analyses of multigenerational families with affective disorders.

Psychological and social theories for female preponderance have also been advanced: women occupy a lower status in society than men; they have fewer opportunities, and may be "trained" or socialized in childhood and beyond to be more passive, more "helpless," more dependent than men. Therefore, they may be more depression-prone. These theories are promising and suggestive, but also as yet unproven.

The question of sex differences and depression is still an open one; as with other indices, sex must be weighed together with other factors to see whether the current ratio continues to hold up across the board in the future, or will change, depending, for example, on subtypes of depression as they are more clearly identified.

Age

It had been thought in the past that the risk for clinical depression increased with age. However, recent studies have found that a high proportion of younger people (under 40) are depressed. Bipolar disorder has an earlier average age of onset (the late 20's) than non-bipolar clinical depressions (middle to late 30's). These disorders also seem to first appear at a younger age in women than in men. Depressive symptoms show a higher prevalence in younger adults (18 to 44 years) than in older ones. One recent study found that depressive symptoms were highest in women under 35, and tended to decrease with age. The peak prevalence for depressive symptoms in men tends to appear in the 55-to-70 age range.

Marital Status

Married persons and those with intimate, nonmarital relationships have a somewhat lower rate of clinical depression than nonmarried persons. No relationship between bipolar disorder and marital status has been shown. With depressive symptoms, however, marital status plays a part that varies depending on the sex of the person. Overall, separated and divorced people show the highest rate of depressive symptoms, and those never married and currently married show the lowest. Ranking from highest rates of depressive symptoms to lowest, the order is as follows:

- separated and divorced women (highest rates)
- single, widowed and divorced men
- single and widowed women
- married women
- married men (lowest rates)

Socioeconomic Status

Whether defined by occupational, income or educational level, or a combination of these, there is strong evidence that depressive symptoms appear more often in people of lower socioeconomic class than in those of higher classes. There is a slightly higher rate of non-bipolar clinical depression in the lower social classes, but the difference is not as great as with depressive symptoms. These findings may reflect different access to treatment depending on social class; the actual number of depressive episodes may not differ. Bipolar disorder appears more in people of higher social classes, often among those of high educational and social achievement.

Race

Rates of non-bipolar clinical depression and bipolar disorder among blacks and whites do not differ. There is no evidence that race, per se, is a factor in rates of depressive symptoms, when socioeconomic status, that is, social class, is taken into account. It appears from recent studies that social class is the determining factor in the rate of these symptoms.

Religion

No differences in rates of non-bipolar clinical depression have been reported among members of different religious groups. Bipolar disorder, however, has been found to be more prevalent in members of certain religions such as the Hutterites, a small, inbred community of Anabaptist Protestants living in the Midwest, and among Ashkenazic Jews (a descriptive term for Jews with roots in eastern or northern Europe). However, increase in rates for these groups may reflect ethnic, genetic or biological variables rather than religion. There has been no relationship found to date between religion and depressive symptoms.

Urban versus Rural Residence

Is it healthier to live in the country, as many of our forebears thought? Or is city life more rewarding and stimulating? In terms of clinical depression, no one knows. In general, studies show higher overall rates of mental illness for urban populations than for rural

ones, but no studies have been done solely on depression. Similarly, little is available in the way of studies on depressive symptoms, although one such investigation found no difference in these rates in rural versus urban settings.

Culture

The question of comparative prevalence of clinical depression in different countries and subcultures is an unresolved one. To some extent, more exact information is dependent on the adoption of standardized diagnoses, so that clinicians and researchers can agree as to exactly what they are talking about when they speak of clinical depression. A study of mental disorders in China, whose research design is comparable with the ECA study, is now being conducted; the cross-cultural information on incidence and prevalence of clinical depression should be valuable. Studies in a number of African countries indicate that physical symptoms accompany depression much more often than in the United States, while expressions of guilt, sadness and self-blame are found much less frequently.

It seems clear that culture modifies the expression of depression, and it may in fact mitigate or change the rate of depression in some groups; exactly how and in what way is not known. It is certainly not a simple relationship, and there is a great deal yet to be learned.

Genetics

The importance of the role of genetic transmission in clinical depression has been increasingly recognized in the past 10 years. There is compelling evidence for hereditary involvement in bipolar disorder, for example. But, as in all facets of the investigation into the causes of clinical depression, the issues involved in genetics become more complex the more closely they are examined.

Studies of genetic transmission rest on epidemiological information. They generally examine either large groups of people or several generations in families where there is diagnosed clinical depression. These investigations have also included the examination of adopted children and twins. An important facet of some of the studies is the search for specific identifying biological factors in clinically depressed people and their relatives. The presence of red-green color blindness, for example, has been thought by some scientists to be associated with bipolar disorder. However, the findings to date have been inconclusive. It would be an important breakthrough if one such biological factor could be isolated. Scientists think that within a generation, perhaps sooner, this will occur with bipolar disorder, but in all likelihood that factor will only be the beginning of the search, and will lead to the discovery of a host of other factors.

In studies of family inheritance it is extremely difficult to separate heredity from environment—the nature versus nurture controversy.

While the pendulum of scientific and public opinion has swung in both directions in the past, current scientific thinking favors a complex intermixture of heredity and environment. For instance, if a women is depressed, and her mother, aunt and grandfather were all depressed, does that mean that depression is "in the genes," or that she has learned the depressive behavior by living in a depressing household? For some people there does seem to be a genetic vulnerability that, given a combination of life circumstances, will develop into a clinical depression. But whether that genetic vulnerability is necessarily present in all people who become clinically depressed is not at all clear. It is clearest in bipolar disorder, but less so in unipolar disorder.

There are behaviors that may run in families independent of any genetic connection. The propensity to let off steam by quarreling loudly, or, conversely, to endure difficulties in silence, for example, may be learned and carried over from generation to generation. Nongenetic conditions such as poverty or wealth may also "run in families," influencing types of behavior. In looking for genetic influences in clinical depression, scientists cannot discount the known adaptability of human beings in a wide range of circumstances. Are there biological markers that can be tied to genetic inheritance? Does transmission occur through only one gene, or through many different ones? Could the vulnerability to depression sometimes be caused by a nongenetic biological factor—a virus, for instance? These are only a few of the many questions that remain to be answered.

Scientists must also take into account whether the population they are studying may in itself complicate or distort the results of the investigation. An ethnically diverse population presents more genetic variables than an ethnically homogeneous one. Complicating environmental issues, even in ethnically similar groups, may include such factors as urban versus rural life and generational differences. "Risk period," the vulnerable age for the illness, must be taken into account. Another issue is assortative mating: people who are clinically depressed, or who come from families with this type of history, may tend to marry other people with similar conditions and family histories.

Population Genetics

Epidemiological studies are being conducted all over the world, in such diverse countries as Sweden, Poland, Australia, Italy and Israel, as well as in the United States to clarify the role of genetic factors in affective disorders. The Scandinavian countries are especially good sources for these studies because the populations are relatively homogeneous ethnically and excellent records exist. In the United States, a study on affective disorders in the Old Order Amish of Pennsylvania has recently been concluded. The Old Order Amish are

a researcher's dream; they come close to being an ideal human laboratory for the genetic study of clinical depression. The Amish are members of an extremely conservative Protestant sect; their ancestors came to the United States from Germany in the 18th century. Since that time, they have remained enclosed within their own communities; they maintain strict separation from the outside world, follow a defined set of customs, marry only each other, have large families, and keep excellent records. Information on their European ancestry is extensive; in fact, all Old Order Amish in the United States (there are 69 other settlements besides the Lancaster one) can trace themselves back to a group of 30 people. In addition, Amish culture severely frowns on the abuse of alcohol or drugs and criminal behavior; therefore these conditions are virtually nonexistent in the population. Preliminary reports suggest that in this group the ratio of unipolar to bipolar disorder is closer than the 10:1 usually found in the American population, and also that the sex ratio (females to males with major depression) is narrower than the 2:1 usually found in the general population.

Family studies (which rely either on one informant or many family members), although subject to many of the methodological problems described earlier, have had some common general findings: first, that the rate of clinical depression is consistently higher in the relatives of depressed people than in the relatives of normal control groups, and second, that people with bipolar disorder tend to have first-degree relatives with both bipolar and unipolar disorder; whereas those with unipolar disorder tend to have first-degree relatives with only unipolar disorder. Scientists believe that there is a partial genetic overlap between these disorders, that is, for some people, the same genetic vulnerability may produce either bipolar or unipolar disorder.

Studies of twins have added to the evidence of genetic predisposition. Identical twins come from the same fertilized egg, and therefore have the same genetic makeup, while fraternal twins come from two different eggs, and only have 50 percent of their genes in common (as do ordinary siblings). Theoretically, if a disorder such as depression is caused by a genetic abnormality, the illness would always be found in both identical twins of a set. However, studies of affective disorder in identical twins show a concordance rate (both twins having the illness) of 40–71 percent, while the rate for fraternal twins is 0–13 percent. The rates are similar whether the twins are raised together or apart, and higher for bipolar than unipolar disorder. One might ask why identical twins don't show 100 percent concordance for the illness. Again, the supposition is that the genetic component is only a predisposition, and environmental factors play a part.

Studies of adopted people may also be helpful. One such investigation has shown that there is a greater incidence of clinical depression found among the biological parents of bipolar adopted adults than found in their adoptive parents. Control groups used were

non-depressed adopted adults, bipolar adults who were not adopted, and the parents of patients with polio.

Unfortunately, very few such studies have been done; more research is needed in this area.

Biological Genetics

Two major types of biological models for testing genetic hypotheses have been developed. *Unitary models* suggest that all persons with a given diagnosis (or set of diagnoses) have a single underlying genetic vulnerability which can be graded on a liability scale. Unitary models can be quite complex: one example is the hypothesis that biopolar disorder, unipolar disorder, dysthymia and related conditions represent gradations of severity of illness stemming from one genetic liability. *Heterogeneous models* suggest that within a diagnostic entity, some cases are caused by one genetic factor, others by a second (and distinct) factor, still others by a third, and so forth. One well-known heterogeneous model theorizes that in some families, bipolar disorder is connected to X-chromosome linkage, while in other families it is not. Investigations using these models can become very complicated, using a great number of variable factors.

More specific studies attempt to isolate one possible variable. Many scientists are concentrating on the search for a *trait marker*, a biological characteristic that is clearly associated with a tendency toward clinical depression. If scientists had an ideal, it would be a trait marker that could be traced to a specific location on a particular chromosome; it would be inheritable; it would be observable in well but susceptible people and recovered ill people, not merely in those who were currently ill; and its presence would be associated with the illness—ill people would always have the marker, while their healthy relatives might or might not. There are two ways of going about the search for markers. One is to look for particular biological characteristics that in themselves may be associated with the illness. Examples of some of the characteristics currently under investigation include monoamine oxidase (MAO) enzymes and metabolites, alterations in cell membranes, cortisol levels, and the Duarte protein, an abnormal brain protein.

The second strategy is to study *linkage* or *association markers*. If two genes are located near each other on a chromosome, there is a good chance that they will be inherited together. Genes that may possibly be linked or associated with clinical depression are currently being investigated. The attempt to correlate color blindness, which is carried by a single gene, with bipolar disorder in some families is an example of this. Other linkage and association studies include investigations of the X chromosome, various blood types, and immune systems. So far, although some of these studies are promising, none have been replicated by a large number of scientists, and so the search continues.

Biology

The workings of the human body have been mapped in a gross sense, but many of the finer points are still unchartered territory. Some actions and interconnections of body organs and systems are just beginning to be explored. For example, recent research indicates that the functioning of the brain is far more complex than had previously been thought; its mechanisms extremely complicated and interactive even on the molecular level. When a disorder like clinical depression occurs, it may be triggered in a number of different places in the body, perhaps in several at once. Physical malfunctions may be set off by a number of factors, outside of the body as well as within it. These interactions are complex and still unclear, and the object of intensive investigation.

The Brain

The brain transmits internal messages by means of electrical impulses. The unit of transmission is the nerve cell, or neuron. There are an enormous number of neurons in the brain; estimates range from 10 billion to a trillion. While neurons vary in size and shape, the prototypical neuron could be described as consisting of a cell body and a number of tentacle-like projections, some of which are primarily senders and others receivers of the electrical charge. In order for this transmission to take place, the neuron produces certain chemicals called neurotransmitters. These travel from the sending nerve cell terminals across a minute space between neurons, called the synaptic cleft, and attach to special sites called "receptors," located at the end of the receiving tentacles of the next neuron. The process of transmission is assisted by electrolytes, and by neurohormones, as well as by other substances. The entire operation is apparently regulated in the most exact way: a specific amount of neurotransmitter is produced for sending purposes, and what is not used is pulled out of circulation and destroyed or rendered inactive by a variety of mechanisms.

This is a complicated process involving a number of actions, and there are a number of places where things might go wrong: in the production of neurotransmitters, in the release process, in the actual transmission, the receiving, or the destruction/inactivation process. Until very recently, most of the information about the living human brain was inferential. New techniques with computers and other sophisticated technology have paved the way for research, but at this time a great deal of our information remains indirect and suppositional.

Researchers in clinical depression have focused their attention on a special class of neurotransmitters called the biogenic amines. The first "amine" hypothesis suggested that a transmitter called norepinephrine was the culprit: too much produced mania, and too little, depression. This was an elegantly simple theory that paved the way

for a great deal of research. It turned out, however, to be too simple: in time it was found that other neurotransmitters — serotonin and dopamine — were also implicated. Later, another transmitter, acetylcholine, came into the picture, and several others are now being investigated. Scientists began to hypothesize that depression might not be the result of the imbalance of just one neurotransmitter, but perhaps might be caused by imbalances among two, three, or several. In addition, research done on other substances involved in neurotransmission, such as electrolytes and hormones, began to be incorporated into this thinking. Currently, researchers hypothesize the possibility of several types of clinical depression, each type based on a series of dysfunctions connected to the firing of certain chains or combinations of chains of neurons. It is known that the neurotransmitters are only the tip of the iceberg (see figure 2).

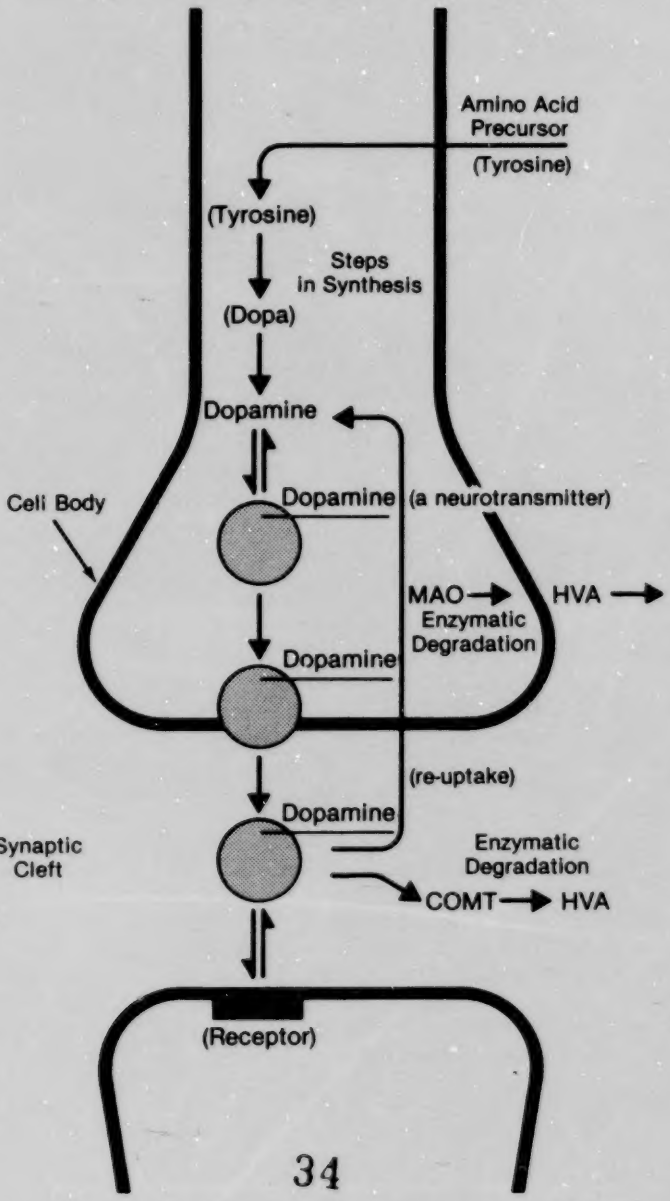
All inferential methods of studying brain activity have their methodological problems. One which has yielded much promising and useful information, however, has been the study of neurotransmitter metabolites. When the neurotransmitter has served its purpose, it is destroyed or rendered inactive in a variety of ways. One way is by conversion to an inactive substance called a neurotransmitter metabolite, which then travels down exit routes in various parts of the body: cerebrospinal fluid, blood, and urine, for instance. The measurement of levels of these metabolites has led to certain suppositions about what is problematic in the neuronal activity of the brain, or, conversely, a scientist may hypothesize a problem, and then test to see if it is borne out in the metabolites of depressed persons. The principal metabolite of norepinephrine is 3-methoxy-4-hydroxyphenyl glycol (MHPG); that of serotonin is 5-hydroxyindolacetic acid (5-HIAA); of dopamine, homovanillic acid (HVA).

Some depressed persons show lowered levels of MHPG in cerebrospinal fluid or urine; others show normal or elevated levels. There appears to be a connection between imbalances of norepinephrine and serotonin in some people with clinical depressions: researchers have found clusters of depressed individuals with low MHPG and high 5-HIAA, and others with normal or high MHPG and low 5-HIAA. One particularly interesting study involved the separation of depressed people into two groups: those with normal 5-HIAA and those with lowered 5-HIAA. Data suggested that the lowered 5-HIAA group was more likely to commit suicide, and in fact, the researchers were able to predict with a fair degree of accuracy which of the depressed persons would no longer be living at the end of a year based on the level of the metabolite. This is, of course, still speculative: there are a number of complex factors that go into an act such as suicide, and scientists are far from being able to predict behavior solely on the basis of body chemicals levels. Nevertheless, it is an intriguing finding.

Dopamine, through its metabolite HVA, is also implicated in

Figure 2

Release and Inactivation of Dopamine, One of the Neurotransmitters.



certain types of depression: some people with bipolar disorder are characterized by high levels of HVA when in the manic state; on the other hand, one subgroup of depressed persons is characterized by low HVA levels.

The action of the tricyclic antidepressant drugs offers further support for the theory of differential imbalance between neurotransmitters in certain types of depression. One class of tricyclics, imipramine, seems to achieve its effect by increasing the level of norepinephrine, while another, amitriptyline, appears to work by increasing serotonin. Given these actions, one researcher has proposed two subtypes of depression:

- Norepinephrine depression: characterized by low MHPG and high 5-HIAA; treated with imipramine
- Serotonin depression: characterized by high MHPG and low 5-HIAA; treated with amitriptyline

These and other findings are still being developed. As can be seen from the variety of findings, scientists are still searching for a large variety of clinical depressions, which may result from the imbalance of a number of different chemicals.

The transformation of neurotransmitters into their metabolites is assisted by enzymes, the principal ones being monoamine oxidase (MAO) in the cell body and catechol-O-methyl-transferase (COMT) in the synaptic cleft. Decreased levels of COMT have been found in some depressed persons, while in those with bipolar disorder, researchers have found varying levels of COMT. In one study, although considerable overlap occurred, one researcher found that agitated depressed persons were more likely to show high COMT levels, while lethargic depressed persons showed low levels. Both high and low MAO levels have also been reported in different categories of depressed people. Low MAO levels have been associated with bipolar disorder.

Research is also being conducted concerning the point of arrival of the neurotransmitters: the receptors. One question that has plagued scientists is the delayed action of antidepressant drugs. Almost immediately after being taken, these drugs block the return of neurotransmitters to the sending neurons, thus freeing more neurotransmitters to carry the electrical impulse. However, in spite of this immediate action, it takes 2 to 3 weeks for the therapeutic effect of the drugs to show in the depressed person's behavior. One hypothesis is that the lag time has something to do with adjustment of the receptors; perhaps changes in their sensitivity to receiving the neurotransmitters or even an actual increase in their numbers occurs during this 2- to 3-week time period.

Electrolytes are substances that carry electric current. Electrolytes in the body, such as sodium, magnesium, calcium and potassium, are directly involved in neurotransmission; thus, imbalances or problems

with electrolytes have been correlated with certain types of clinical depression.

Lithium, a naturally occurring element used to treat bipolar disorder, contains many properties in common with the electrolytes present in body tissue and fluids. Researchers have confirmed that lithium competes with or substitutes for one or more of these electrolytes, and in this way seems to correct imbalances. Recent research has focused on the cell membrane, using the red blood cell as an analog to the supposed action at the neuron site. Scientists hypothesize that persons with bipolar disorder have problems with the transportation of sodium across the cell membrane. It has been thought that various problems of this sort may be genetically determined. This is, however, still a preliminary finding. Lithium has many actions, and its electrolyte-like effect is only one of them. Nevertheless, it provides an interesting model for the supposition that electrolyte problems may set off a host of other difficulties in neurotransmission.

Neuroendocrine System

Several endocrine disorders have provided models for depression: Hypothyroidism, a disorder of low thyroid production, manifests with a depressive condition characterized by lethargy. Cushing's disease, a disorder of the adrenals, is also often characterized by depression. Gonadal hormone changes are thought to be implicated in depression; premenstrual syndrome may provide a model for hormonally associated depressions in women.

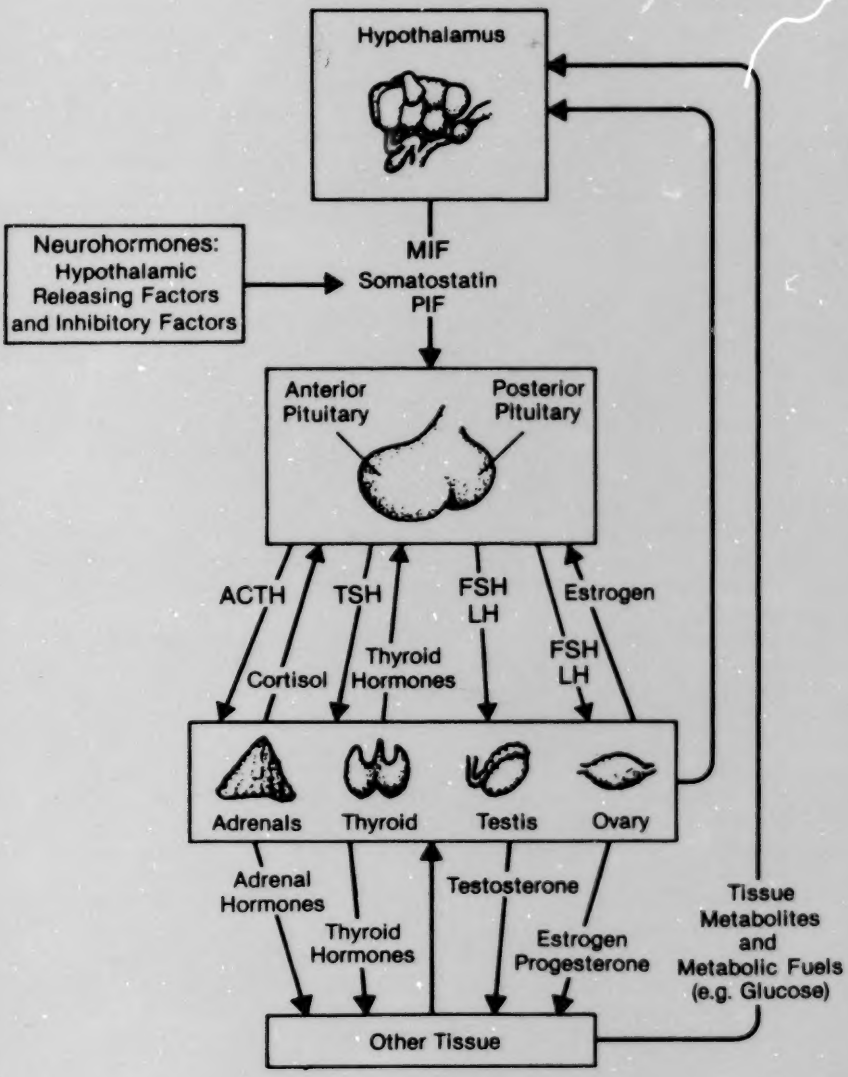
There is a complex interaction between the brain and the various glands (pituitary, thyroid, parathyroid, pineal, adrenals, pancreas and gonads) that compose the endocrine system. Messages are transmitted via hormones produced in the glands and also by analogous neurohormones (produced in the brain). Classically, research has focused on the glands and their production and distribution of hormones to various organs in the body, but increasingly, scientists studying depression are concentrating on neurohormones and their pathways to the glands.

Neurohormones are produced mainly in the hypothalamus by special cells that are stimulated by neurotransmitters. These neurohormones then travel to the pituitary gland, where they stimulate the release of pituitary hormones, which then travel to other glands, where they in turn stimulate the release of various glandular hormones (see figure 3).

Raised and lowered levels of various neurohormones and glandular hormones are being studied in association with depression. Growth hormone (GH), secreted by the pituitary gland, is released following the insulin tolerance test. GH in response to this test has been found to be dramatically lower in some depressed persons than in nondepressed

Figure 3

THE HYPOTHALAMIC -PITUITARY AXIS AND ENDOCRINE SYSTEM



control groups. Low levels of luteinizing hormone (LH) have been found in some depressed women. Some depressed persons, particularly those with major depressions, show a diminished level of thyroid-stimulating hormone (TSH).

A large amount of research has been done concerning the connection between the hypothalamus, the pituitary, and the adrenal glands. Cortisol, a hormone produced by the adrenals, is significantly raised in some people with major unipolar depression. The secretion of cortisol is controlled in part by a pituitary hormone called adrenocorticotropic hormone (ACTH), whose level is also shown to be higher in this category of depressed persons.

Many researchers feel that imbalances of neurotransmitters trigger consequent imbalances of neurohormones, with the process continuing down the line. There is a supposition, for instance, that a deficiency of norepinephrine or serotonin leads to an imbalance in the release of the neurohormone corticotropic releasing factor (CRH) in the hypothalamus, which then leads to an imbalance in the release of ACTH in the pituitary, which in turn leads to an overproduction of cortisol in the adrenals.

Another hormone which is exciting research interest is melatonin, which is secreted by the pineal gland. Its function in humans is still not exactly known, but its synthesis is triggered by darkness and its molecular structure strongly resembles the neurotransmitter serotonin, from which it is derived. Seasonal variations in the production of melatonin are now being studied for their possible connections to seasonal mood changes and more severe seasonal episodes of mania and depression.

Vasopressin, a neurohormone manufactured in the hypothalamus, is also being studied because of its role in regulating electrolyte balance and in altering memory functions, both of which are interfered with during depressive episodes.

Promising investigation is being done with various peptides, the enkephalins and endorphins, which seem to function both as neurotransmitters and neurohormones. They appear to act in a similar fashion to opium or morphine in relieving pain and creating pleasurable feelings; further research into their function may provide more knowledge about the causes and treatment of depression.

It is hoped that eventually biological research will lead, among other things, to tests that will diagnose or confirm clinical depression. Four tests have been devised which are currently available to clinicians: the dexamethasone suppression test, the MHPG assay, the thyrotropin releasing hormone (TPH) stimulation test, and the sleep electroencephalograph. The application of these tests for clinical purposes is still controversial. At present, their diagnostic efficiency is either limited or questionable, and none can substitute for a rigorous clinical examination. Their current promise is as research tools to help scientists understand more about depression.

Psychophysiology

Psychophysiology, which includes such areas as electroencephalogram (EEG) measurements, sleep studies, and the observation of biorhythms, is a useful component in the study of clinical depression. The techniques employed are noninvasive, relatively simple to use on depressed human subjects, and also reliable. These studies represent a kind of "fine tuning" of some aspects of behavioral psychology and a check on certain molecular biological studies, as well as being informative in their own right. One current use of psychophysiology is to identify subtypes of depression.

Problems with sleep are common in clinical depression; EEG findings, in combination with other techniques, are being used to identify subtypes of depression connected with sleep patterns. One researcher has found that people who respond to treatment with tricyclic antidepressants and electroconvulsive therapy show specific changes in EEG sleep patterns not shown by nonresponders to these treatments.

Various changes occur in sleep during depressive episodes. Clinical depression is associated with a reduction in deep, slow-wave (delta) sleep, but this is not a specific indicator, since delta sleep reduction is common to other disorders, both psychiatric and physical. More significant are findings of variations in rapid-eye-movement (REM) sleep. For example, increased REM activity and shortening of the usual time interval between the start of sleep and the first REM period have been found in people with major depressions. An antidepressant drug, amitriptyline, has been found to reduce REM sleep time and increase the time between sleep onset and the first REM period. REM deprivation is reportedly effective in treating clinical depression, but the reason for this is not yet known.

The study of biorhythms is one of the most fascinating aspects of physiological psychology. Rhythms — tidal, seasonal, planetary — occur throughout nature. It has been shown that human beings, as well as animals, have internal clocks that regulate a number of functions, some synchronized with the outside world, and some operating only according to an internal monitor. The existence of cycles of sleep and waking, temperature and behavior, even of the minuteness of hormonal secretion and neurotransmitter activity has been demonstrated. It is a logical supposition that disturbances in these cycles would contribute to a variety of disorders including clinical depression.

Much still remains to be learned in this area, but information is steadily increasing. Animal studies of sleep/wake cycles suggest that there is a regulator for this function located in the hypothalamus. Daily and seasonal changes in activity levels of neurotransmitters and neuroendocrines are connected to the secretion of the hormone melatonin by the pineal gland.

In terms of circadian, or daily cycles, current research indicates

that there are at least two potentially separate driving oscillators in humans: a stronger and more stable one that controls temperature, adrenal neuroendocrines, and REM sleep, and a weaker, more fluctuating one that controls the sleep/wake cycle. Sometimes these oscillators operate together; sometimes they move out of synchronization. An example of the latter is jet lag, which occurs when people change from one time zone to another very quickly: the weaker sleep/wake cycle adjusts within a day, while the stronger temperature cycle takes several days to shift. The discomfort people experience in between is the jet lag.

Some researchers have theorized that dissociations of these oscillators may be responsible for certain types of clinical depression. People with bipolar disorder who cycle rapidly (more than four times a year) from mania to depression have been proposed as having an "oscillator" that runs too fast. Other bipolar subjects have shown circadian disconnections between temperature and motor activity, as if normal rhythms were no longer locked into the ordinary 24-hour cycle.

If some clinical depressions are connected to disturbances in these cycles, would attempts to shift or manipulate the cycles be a treatment alternative? Researchers have been attempting to answer that question, with some intriguing results. Experiments have been done to change the length and onset of sleep/wake periods in people with major depressions. One such study compared two groups of depressed people who were studied while they underwent deliberate partial sleep deprivation: one group slept from 9 p.m. to 2 a.m. and the other group slept from 2 a.m. to 7 a.m. The group that went to sleep earlier tended to become less depressed. Speculation about this difference in the two groups has centered around cortisol, whose secretion switches from lowest to highest levels around 4 a.m. It is thought that being awake at that time may help in some way to adjust the cortisol secretion of certain depressed people.

Another study was done with a group of rapid-cycling depressed persons, who were shown to switch from depression to mania or hypomania if kept awake for 48 hours. Some bipolar persons treated with antidepressants and MAO inhibitors developed more rapid cycling, which suggests that these medications also have some effect on the mechanisms that adjust the cycles.

There are also longer biorhythm cycles. Seasonal cycles in clinical depression have stirred research interest. One particularly intriguing investigation involved the study of a group of people with a variant of bipolar disorder that is seasonally connected: these individuals become clinically depressed in the fall or early winter, and hypomanic or manic in the spring or early summer. The researchers speculated that changes in light have something to do with the cycle; this was supported by many of the subjects' anecdotal reports that their condition worsened the further north they moved, and that trips to

Florida or the Caribbean in the winter would snap them out of the depression, which would reoccur when they returned home to the North. Light-therapy exposure twice a day to a very bright light source in fact did bring a sizable number of this group out of their depressions within 3 days; if treatment was discontinued, they relapsed about 3 days later. A number of these people are now using light therapy on their own. Does this mean that winter vacations to the Caribbean will eventually be counted on tax returns as a therapeutic medical expense? Probably not. All of us, normal as well as depressed, respond to the cues of increased and reduced light, and tend to become more active and energetic as the days grow longer and less so as they grow shorter. Light therapy, in the form of high-intensity lamps, holds out promise to people with clinical depressions who seem to respond with special sensitivity to light cues, as many in this bipolar group did. It is potentially a useful form of therapy, nonintrusive and inexpensive. Investigators are also looking into the development of a drug that will mimic this therapeutic light effect.

Health and Physical Illness

There is a close relationship between the state of health and clinical depression. First of all, keeping healthy in general, that is, getting enough of the right kind of food, enough sleep, and sufficient exercise, while no guarantee against clinical depression, may help in preventing some types of depression and certainly keeps the body in a better state to deal with the disorder. Research is now being done to examine the brain's own production of "mood-elevating" chemicals — the endorphins — which may be enhanced by exercise, among other things.

Clinical depression can be produced by certain physical illnesses, and is associated with others. Among illnesses known to cause depression are Addison's disease; Cushing's disease; thyroid disorders; diabetes; some neurological disorders and chronic brain syndromes related to arteriosclerosis; syphilis; multiple sclerosis; and certain vitamin deficiencies. Many illnesses are associated with depression (that is, they are not known to "cause" depression, but the two conditions are often found together): infectious diseases such as infectious hepatitis, influenza, mononucleosis, and rheumatic fever; anemia; malignancies (particularly cancer of the pancreas, leukemia, and brain tumors); endocrine disturbances such as hypoglycemia; uremia; congestive heart failure; ulcerative colitis; rheumatoid arthritis; and asthma. This list is not exhaustive, merely indicative. When a clinical depression occurs or is suspected, a medical checkup is a good idea, especially in the case of older people, so that a physical illness can either be identified and treated or ruled out as a possibility (see table 1).

A number of medications can cause clinical depression, or seem to

Table 1

PHYSICAL ILLNESS AND DEPRESSION

Diseases and Organic Disorders associated with **Depressive Symptoms/Syndromes**
(this list is not exhaustive)

Asthma
Addison's Disease
Congestive Heart Failure
Chronic Brain Syndromes
(related to Arteriosclerosis)
Diabetes
Endocrine Disturbances
Hyperthyroidism
Hypothyroidism
Idiopathic Parkinsonism
Infectious Hepatitis
Influenza
Intermittent Porphyria
Metabolic Problems
Malignancies (esp. Cancer of the Pancreas, Leukemia, and Brain Tumor)
Multiple Sclerosis
Neurological Disorders (some)
Pernicious Anemia
Rheumatoid Arthritis
Syphilis
Systemic Lupus Erythematosus
Uremia
Ulcerative Colitis
Vitamin Deficiencies (some)

Drugs associated with or causative of **Depressive Symptoms/Syndromes**

Class and Generic Name	Trade Name
ANTIHYPERTENSIVES	
Reserpine	Serpasil, Ser-Ap-Es, Sandril
Methyldopa	Aldomet
Propranolol hydrochloride	Inderal
Guanethidine sulfate	Ismelin sulfate
Hydralazine hydrochloride	Apresoline hydrochloride
Clonidine hydrochloride	Catapres
ANTIPARKINSONIAN AGENTS	
Levodopa	Dopar, Larodopa
Levodopa and carbidopa	Sinemet
Amantadine hydrochloride	Symmetrel
HORMONES	
Estrogen	Evex, Menrium, Femest
Progesterone	Lipo-Lutin, Progestasert, Proluton
CORTICOSTEROIDS	
Cortisone acetate	Cortone
ANTITUBERCULOSIS AGENT	
Cycloserine	Seromycin
ANTICANCER AGENTS	
Vincristine sulfate	Oncovin
Vinblastine sulfate	Velban

be connected to its symptoms. Among these are antihypertensives, such as reserpine, methyldopa and others; antiparkinsonian agents such as L-dopa; corticosteroids, especially cortisol; female hormones such as estrogen and progesterone (found in oral contraceptives among other medications); antituberculous agents; and immunosuppressive anticancer drugs. There may be a link between certain types of foods and beverages and depression. For instance, caffeine-containing substances such as coffee, tea, chocolate, and some sodas can lead to a syndrome of agitation and shakiness and, when withdrawn, a depressive condition may result.

The relationship of vitamins to depression is a largely uncharted one. For women who experience clinical depressions as a result of taking oral contraceptives, vitamin B-6 (pyridoxine) has been given in certain research studies. Some researchers found it to be effective in alleviating depression, while others did not. More research in general on vitamins and foods as they relate to depression is needed.

Psychology: Personality, Cognition, and Behavior

Theories and observation in psychology have contributed significantly to a greater understanding of possible causes of clinical depression. Observation of the behavior of both humans and animals has increased knowledge about the biology and causes of depression as well as the effects of therapy.

Personality

The term "personality" is used by researchers to refer to characteristic modes of behavior which may be constitutional or acquired during development. According to theorists, certain personality traits or sets of traits may create a vulnerability to depression, may affect the symptoms or the course of the depressive episode, or may occur as a result of the depression. In addition, a set of personality traits may be a manifestation of a genetic "endowment" or predisposition to clinical depression. Here, the condition is considered to be a continuum, with the personality set at the "mild" end and the depressive disorder at the "serious" end. None of these theories are mutually exclusive, in fact, they are often interconnected in research.

Historically, psychoanalytic theorists have considered the personality traits of undue interpersonal dependency and low self-esteem important to predisposing an individual to clinical depression. Reliable, standardized research on human depressed subjects that would either validate or contradict this view is only beginning; to date there has been only one such study, described later in this section. The strongest scientific link at this point between depression and dependency rests with the work of students of animal behavior.

Interpersonal dependency, in its broadest sense, refers to thoughts, feelings, and behaviors connected with associating, interacting, and relying upon other people, and is a part of the normal human personality structure. Scientists have related interpersonal dependency in humans to attachment bonding in mammals. Studies of primates and of human infants suggest that attachment bonding, the connection between the infant and the mother or mothering figure, is promoted by inherited traits and is vital for individual growth and for biological survival of the species. The relatively long period of infant helplessness and dependency in both primates and humans provides the opportunity for social communication, learning, and group interaction. Severing or disrupting such bonds can have serious depressive consequences. Scientists have studied such situations in animals in order to reach a better understanding of depression in humans. However, while depression in animals can be considered analogous to depression in humans, it should not be seen as identical.

One such research model is the *separation syndrome*, a naturally occurring depressive behavior pattern in animals, especially primates, which has been observed closely. The syndrome consists of two phases: *protest*, characterized by crying, screaming and random activity, and *despair*, characterized by lessened social contact, slow movement, dejection, and stupor. The primate reaction to maternal separation parallels that of human infants parted from their mothers. Separation in primates is very serious; although responses vary across species and with different age groups, the condition often leads to abnormal behavior and death.

Researchers studying animal separation behavior under laboratory conditions have intensified the animals' responses by lowering levels of certain neurotransmitters. Physiological alterations that occur, such as sleep changes and slowing of body movements, are similar to those seen in human depression. Finally, the animals are given "treatments" that parallel current human treatment, such as ECT, tricyclic antidepressants, and animal "therapists," which are helpful in reversing the condition.

In humans, attachment bonding has profound and far-reaching consequences beyond biological survival; some theorists have connected it to the development of emotion. Various problems with dependency or difficulty in getting dependency needs met may lead to a clinical depression.

Low or fragile self-esteem, or the loss of self-esteem are also thought to be connected with depression. Some theorists have linked unmet dependency needs to loss of self-esteem; others feel that loss of self-esteem may be connected to other issues.

There has been some speculation that the increased dependency observed in depressed people is a function of the disorder, rather than a long-standing personality trait. To test this theory, scientists would have to follow a group of nondepressed subjects for a number of

years, assess their personality characteristics, and correlate these with those who did or did not become clinically depressed. This is an elaborate and complex type of investigation which to date has not been attempted.

One recent research study did show, however, that a group of women with recurrent major nonbipolar depression showed higher levels of interpersonal dependency than the norm, even when not nondepressed. Their dependency was characterized by an increased need for recognition and approval, excess vulnerability to being hurt, and extreme dependence on a single other person. However, even more marked than dependency in these women was social introversion.

Introversion, together with neuroticism, are two sets of traits that scientists in the past few years have discovered to be meaningfully correlated with certain types of depression. As defined by researchers, being introverted means being withdrawn, shy, reserved, serious, deliberate, and controlled; neuroticism is a set of traits that includes moodiness, nervousness, the liability to break down under stress, and the tendency to ruminate and to be easily upset.

Recent research has concentrated on subtypes of depression; one important subtype is the depression characterized by somatic symptoms. One study found that, after recovery from the illness, depressed pressed subjects without marked somatic symptoms were significantly more neurotic and introverted than those with somatic symptoms. The latter were close to the norm on these traits. Several studies dealing with subjects recovered from both bipolar and nonbipolar depression with somatic symptoms showed both groups to be about at the norm for neuroticism and introversion. In these and other studies, there is evidence to suggest that people whose depressions were secondary to other illnesses and those whose depressions were not marked by somatic symptoms may have been predisposed to depressive episodes by personality characteristics such as neuroticism, introversion, anxiety, and low self-esteem.

Another theory holds that certain personality patterns are subclinical, or extremely mild, versions of more serious disorders. In this model, for example, a cyclothymic personality, characterized by mood swings, would be a mild version of bipolar disorder. Genetic investigators are pursuing this possibility, on the supposition that certain temperaments may be hereditary and appear in both well and ill family members, but no conclusive evidence has yet been presented.

Behavior and Cognition

A number of behavioral theories have been advanced to explain clinical depression. The learned helplessness theory connects depression to repeated failure to control one's environment in an advantageous way. Recurrent punishment or the absence of positive reinforcement, along with repeated attempts to control or avoid the

situation, result in passivity. Some researchers think this theory may give clues about certain types of depression in women, who are generally trained to be more passive than men, and are often either not rewarded or punished for attempts at environmental mastery.

The learned helplessness theory was originally developed on animal models such as dogs and rats. One basic experiment involved giving dogs an electric shock. If the dogs were unable to alter or prevent this shock, they became apathetic and withdrawn, and later failed to respond even when the shock became avoidable. Thus, the dogs appeared to have "learned" to be helpless. The repetition of this experiment with different types of animals has shown that the learned helplessness effect results from the animal's inability to control the shock, rather than from the shock itself. Neurochemical changes resulting from learned helplessness have been found to be similar to those in animal separation loss. Therapy for this condition in animals includes "unlearning" and drugs such as antidepressants.

Self-control theory maintains that clinically depressed people have problems because they pay more attention to negative events than to positive ones, focus on immediate rather than longer term consequences of behavior, are overly hard on themselves, attribute success to outside forces and failure to their own lack, and in general, reward themselves too little and punish themselves too much.

Cognitive theory, in some ways similar to self-control theory, suggests that distorted thinking is central to clinical depression. This type of thinking can be described briefly as a view of the world as cruel, the self as deficient and unworthy, and the future as hopeless. The cognitive model suggests that this type of thinking is developed early in childhood, and leads to greater susceptibility to depression during stressful periods later in life. Cognitive distortions include logical errors, misinterpretation of events, and overgeneralization.

Research on cognitive deficits in clinical depression has shown that in fact, depressed people do show interference with ordinary ways of thinking. Poor concentration, memory loss, inability to make decisions, and confused thinking are real problems connected with clinical depression, not merely deficits the depressed person is imagining because he or she feels so dismal and self-deprecating. Material learned when a person is in a depressed or manic state may not be remembered later on.

Reinforcement theories hold that depression is connected to few positive rewards and many negative "reinforcements." Another observation is that depressive behavior may elicit sympathy and attention at first, which in itself is a kind of positive "reinforcement" of negative behavior, but that eventually people may tire of the depressed person's attitude and complaints, leaving him or her with fewer social outlets and fewer positive rewards. Not enough positive reinforcement, or too much anxiety attached to potentially rewarding behavior may lead to a kind of downward spiraling effect. The

depressed person's attempts to socialize, when not met with success, may lead to fewer attempts, less success, and less desire to make more attempts. Depressed mood has been correlated with a decrease in activities, social deficits, shorter communications, and smaller social networks.

As observations of the condition and actions of clinically depressed people these behavioral models are promising, but whether the behaviors and thought processes are the "cause" or the "result" of depression, or perhaps both, is unresolved.

Life Events

The term "life event," as used by researchers, refers to a change in a person's social circumstance that causes a disruption in the customary pattern of living and requires adaptation. A life event can be desirable (a job promotion) or undesirable (the death of a loved one). It can also be defined in a number of other ways: whether or not it can be controlled by the individual; whether it is an "entrance" type of event (such as the birth of a baby), or an "exit" (such as a divorce); anticipated or unanticipated; major or minor; involving other people or only oneself; short term or long term; recent (occurring within the last 6 to 12 months) or remote (such as the death of or separation from a parent in childhood). Areas that encompass life events can be roughly broken down into health, work, home and family, personal and social, and financial.

Researchers have found that certain kinds or clusters of life events can cause or trigger clinical depressions. A number of studies have shown more "exit" events (such as the loss of a significant person through death or separation), more undesirable events, more "severely threatening" events, and more uncontrollable events in the 6 months prior to the onset of clinical depression than in nondepressed control groups or in groups with other psychiatric disturbances.

One study showed that clinically depressed people who responded poorly to tricyclic antidepressant drugs treatment were having more undesirable, health-related, and uncontrollable life events during treatment than people who responded well to the drugs.

One researcher, studying the relationship of life events to depression in women, identified four "vulnerability factors" that appeared to increase the likelihood of a depressive episode in the face of a stressful life event or events. These were unemployment, three or more children under the age of 14 at home, lack of a confiding relationship with a partner, and childhood loss of a parent through death or separation. All four of these factors are presumed to contribute to depression by rendering an individual less able to cope with stress. Research studies based on this model have not supported it as a whole, although in some investigations certain aspects of it, such as the lack of a close confidant among women (but not men) have been

associated with depression. It is still not clear, however, whether specific "vulnerability factors" cause depression or merely interact with it.

Depression itself may also cause stressful life events to occur. For example, a woman may become depressed following a divorce. She is irritable and begins to isolate herself. At first her friends rally around her, but as months go by, her behavior alienates many of them. Her lack of sleep and inability to concentrate interfere with her work; she is eventually fired from her job. When she emerges from the depression, perhaps a year later, she has lost not only her husband, but also her job and many of her friends. Whether this kind of pattern can actually be traced in clinical depressions is an area of research speculation. Most research to date has been done on events preceding depression, and not a great deal on events that may interact with depression, or life events that depression may cause. There have been no correlations found to date between various subtypes of depression and negative life events. Further, negative life events are not always connected to depression: some depressions develop without an apparent precipitating event, while other events are endured without being followed by a depressive episode.

Chapter 3

Special Age Groups and Depression

Children

Research in clinical depression in childhood is only beginning. One of the first questions researchers are asking is precisely how childhood depression manifests itself. Two syndromes similar to adult depression have been identified: one in infancy, and another in prepubertal children. However, some researchers think that yet other different types of disturbed child behavior may constitute special kinds of childhood depressions, unlike those of adulthood. Childhood psychopathology, a broad category that includes a range of disorders and serious clinical problems, is estimated to be present in about 12 percent of the nonadult population. Estimates of clinical depression are extremely variable and depend on the age groups being examined. In contrast to prepubertal children, adolescents develop clinical depressions with symptoms very similar to those found in adults.

A depressive condition can exist as early as infancy; it is called the "nonorganic failure to thrive" syndrome. As the name implies, babies with this condition are unresponsive to external movements such as eye contacts, tend to cry weakly, refuse food, sleep excessively, and appear apathetic. This syndrome has been associated with inadequate care in the environment; it is seen as somewhat similar to the "despair" shown by infant monkeys separated from their mothers, as described by ethnological researchers. How this condition relates specifically to later childhood or adult clinical depression is not known.

From toddlerhood to puberty, it is possible that clinical depression may occur. The manifestations may be similar to adult depression, or it may, some researchers think, be insidious and unclear in onset and show more diffuse symptoms. These are the words of a frustrated, angry 4-year-old, spoken to himself in his bath:

He ain't gonna do nothing.

He's just sitting there forever.

He won't eat his peas or his meat or even his cake.

He won't take candy or gum or be their friend.

He will shut them up in the closet and let them quit breathing.

He don't have to do nothing but sit in the yard all day long.

If they call him to come in, he won't hear them at all, and if they yell at him, he'll just laugh.

He won't do nothing, and they can't make him do what they want him to do.

He'll stick out his tongue at them, and tell them "no."

And he'll just play in the yard all day long.

This child is especially articulate; more often, children will not express their thoughts or emotions unless encouraged. There are several clues to possible depression, some of which are noted by the young poet above. A loss of appetite or refusal to eat previously favored foods, sleep problems such as difficulty getting up in the morning, fatigue, lethargy, and difficulties in school when there was prior interest may be indicators. The child may seem irritable or irascible, snappish, difficult to please, or withdrawn and sulky, quiet, moody and sad. In extreme cases, although this is rare, young children have expressed a wish to die or to kill themselves.

Stressful events play a part in children's depressions just as they do in adults'. Loss of a parent or sibling, illness, divorce, or a move to a new home are the obvious "big" factors; others that may escape an adult's notice include teasing from peers, lack of friends, or a bad experience with a teacher. Physical or emotional immaturity compared to peers, or ineptness at sports when sports are an important part of the environment can also be contributing factors.

Specific treatments such as psychotherapy and medication are by and large not given to children except in cases of serious depression. Some studies have shown tricyclic antidepressants to be effective in severe cases, but these are preliminary findings. In most cases, the clinician will suggest changes in the child's environment: ways to increase his or her self-esteem, promote friendships, get more attention, or resolve school difficulties.

Increasingly, research attention is being focused on the children of parents with a diagnosed major depression. These children constitute a "high-risk" population for depression themselves, although whether this risk is associated with genetic or environmental factors, or a combination of both, has not been determined.

Does depression show itself differently in girls as compared to boys? Are there different rates of depression in girls and boys? The answer is not known. More adolescent girls than boys are diagnosed as being depressed, and more attempt suicide, but a greater number of adolescent boys actually commit suicide. Research on this subject

is just beginning. The current finding that depression is twice as common in adult women as in men gives rise to the question of when this numerical imbalance really begins to appear, and to what extent children who are depressed become adults subject to depression. Anorexia (self-starvation and extreme weight loss), a condition that is found almost exclusively among females and often first seen in the teens, has been associated with depression by some researchers.

While some investigators are concentrating on studying depressions in children that are analogous to those in adults, others are examining the possibility that the symptoms of childhood depressions will differ depending on the child's developmental stage; they are using the theories of Jean Piaget as a framework.

The Elderly

Depression as it relates to aging is becoming a more pressing concern of Americans as our society has an ever-larger percentage of elderly; persons 65 and over now constitute 10 percent of the population, a proportion that has doubled since 1900. If current birth and death rates continue, an increase to 15 percent is expected by the early part of the 21st century.

Depressive symptoms are reported by almost 20 percent of elderly Americans. However, the true incidence and prevalence of clinical depression in this population is not known. The diagnosis of depression seems to be made more frequently for persons under the age of 60 than for those 60 and over, but this finding may be compromised by the unknown number of elderly who are misdiagnosed as having senile dementia, or whose depression is concurrent with or caused by physical illness or multiple medications. For those with a history of unipolar or bipolar disorder, acute depressive episodes seem to increase in frequency with age, although manic episodes appear to be less frequent.

In the elderly, the factors associated with the onset of clinical depression assume a different order than in early or midlife adulthood. Physical health and illness are of paramount importance. Life events, particularly multiple losses and role changes such as retirement, are pressing concerns. Biological factors, such as changes in certain chemical levels that occur with aging, may be implicated in the expression of depression.

In ancient China and in many American Indian tribes, the aged were valued as wise counselors. What they lacked in bodily vigor was more than compensated for by their vast experience, accumulated over a lifetime. For these people, old age was a time of life to look forward to, a culmination of existence. Western culture has by and large not given this kind of respect to the elderly. Contemporary American society is among the most insistently youth-oriented; old age is even regarded by some as a "disease" in itself. Given this orientation,

perhaps it is not so surprising that there is much depressive symptomatology expressed among the elderly; perhaps what is really surprising is that there isn't more.

Close to a third of the suicides in the United States are committed by people over the age of 55. That's a powerful statistic, particularly considering that a large percentage of suicides are committed by people who are clinically depressed. The "high-risk" picture of the elderly suicide completer is that of a white man, aged 55 to 70, who is retired, widowed or single, living alone, and has a history of physical illnesses and possibly alcohol abuse. Suicide, for some, is the bitter end of clinical depression, and while only a small percentage of the elderly actually do commit suicide, it is instructive to see how this "high-risk" profile represents an extreme kind of cumulative loss: an older man (whose employment status traditionally had defined him more meaningfully than it would an older woman) has lost the work role, his spouse, probably many social supports, and his health as well. Many of the clinically depressed elderly who do not commit suicide fit somewhere along this continuum.

Interpersonal losses increase significantly with old age as loved ones die and children are often far away. For some, losses may follow each other in such close succession that it becomes impossible to separate the normal grief process from a chronic depressive condition. For those who have had a minor clinical depressive disorder throughout their lives, the falling-away of social supports may exacerbate depression-connected character traits. Role and status losses, for example, no longer having a job, or what is perceived as a useful function in society, can also contribute considerably to clinical depression, as can financial problems, a serious issue for many of the elderly on fixed incomes. There is some speculation that losses have a negative effect on the human immune system, but research on this question is still in its early stages.

Within this larger picture of incremental losses among the elderly must be placed the strong interconnections between physical illness and clinical depression. Bodily frailty, and its concomitant physical deterioration, inevitably increase with age (over 80 percent of people over 65 have at least one chronic illness), although the rate and severity of these depend to a great extent on the individual. It is also more socially acceptable to complain about physical problems than psychological ones.

An elderly depressed person coming into a doctor's office is likely to present a number of physical complaints. It is unusual for older people to speak of guilt or sadness as younger depressed people often do; more often the depressed elderly are pessimistic, apathetic, and complain of memory loss and sleep difficulties. The physician begins by assessing the problem, and may start with a thorough physical checkup, including a range of laboratory tests, and a complete history. An elderly person may have a physical illness that is causing

depression, such as a thyroid disorder, Addison's disease, or congestive heart failure. There may be a low-level physical disorder which is contributing to depression. Medication being taken for another illness such as hypertension may cause a depression. Depression may coexist with a physical illness, perhaps as a result of perceived loss of functioning or mobility. A mandatory requirement when interviewing an elderly person who is suspected of having a clinical depression is a complete review of all medications: doctor-prescribed, over-the-counter, and "home" or "folk" remedies. Some elderly people keep their own private pharmacies, often collecting items for years and dosing themselves. Combinations of drugs and/or other substances, whether self- or doctor-prescribed, can lead to depressive reactions among other adverse responses.

Depression in the elderly is sometimes misdiagnosed as senile dementia. In addition, sometimes a depression exists along with senile dementia. It is often difficult to tell the difference between clinical depression and dementia in the elderly, although depression more often has a clear onset and dementia an insidious one, and depressed elderly people may complain more about memory loss than those with dementia, but actually score higher on memory tests. Confusion, uncooperativeness, and unsociability are more characteristic of someone with senile dementia. Clinical depression should be looked for as an independent entity, treated separately from dementia, and a diagnosis of dementia cannot be assumed to be a more or less "inevitable" corollary of late life. However, when clinical depression does accompany dementia, treating the depression can enhance the quality of life for the person with dementia.

Depressed persons who have "pseudodementias" are sometimes institutionalized and deteriorate rapidly. One of these pseudodementias, called the "tea-and-toast" syndrome, occurs when an elderly person becomes depressed, withdraws, and starts to subsist on very little (often literally tea and toast). He or she then develops malnutrition, and the combined symptoms can mimic dementia. Because often inappropriate institutionalization can have tragic and irreversible social results, attempts should be made to provide elderly people with the social supports — including nutritional services — that permit them to be treated on an outpatient basis as much as possible.

Various biological factors may be implicated in depression in the elderly. One theory links the occurrence of depression to lowered levels of the neurotransmitter norepinephrine, which is destroyed by an enzyme called MAO, present in higher levels in the aged. Changes in thyroid and pituitary function and increased levels of stress in the elderly have also been theorized to be connected with the prevalence of depression. At this time, however, with the elderly as with all other age groups, multiple causes of different types of depression are assumed. There may well be a different balance of factors operating in a 70-year-old person who gets clinically depressed for the first time as

compared to another 70-year-old who has experienced sporadic, recurrent depressive episodes in the past.

There are many techniques to treat depression in the elderly: psychotherapy, antidepressant drugs, ECT and combined treatments. Research continues to test and develop specific "packages" of treatments geared toward the special needs of the elderly. Clinical depression usually responds to treatment in later life, just as in younger age groups.

Chapter 4

Suicide

She was 55 when she died. She looked behind her and saw a wasteland, never willing to accept that she was loved by many and had richly contributed to the lives of friends, family and strangers. She perished because she allowed herself to be deceived by her own mind into believing she was worthless. She refused professional help because, like many of her generation, she felt it was shameful to seek psychiatric aid. She was consumed at the end by unbearable depression. The best thing she could do for others was to remove herself from their presence—permanently. She could not have been more wrong.

So speaks a women about her mother. Both had manic-depressive illness, but one chose death and the other life. Anne-Grace Scheinin felt so strongly about her mother's suicide that she herself, although she had attempted to commit suicide a number of times, became determined to live no matter how severe her depressions were, and more than this, published her story in an article in *Newsweek* magazine.

Suicide is a major cause of death in the United States. Fifty-five thousand suicides are reported every year, but researchers think that the actual rate may be as high as 75,000 because of unreported suicides, deaths from "suspicious" causes, and some single-car accidents. The suicide rate is on the rise. In the last 25 years, the rate for adolescents and young adults between the ages of 15 and 24 has increased three-fold.

While all suicides are not committed by those diagnosed as clinically depressed, and all clinically depressed people do not attempt or commit suicide, there are marked correlations between the two. Researchers estimate that between 30 and 70 percent of suicides are completed by people diagnosed as having a major depression. Fifteen percent of people with major depressions commit suicide.

Who actually commits suicide? Who makes attempts? Are the attempters similar to those who complete the act, or not? If a person thinks about suicide, is he or she likely to go on to make the attempt? These are the questions that scientists continue to ask. Preliminary profiles of suicide attempters and those who complete suicide have been developed, but there is still a long way to go.

In terms of suicide in the clinically depressed, more women try, and more men succeed. The depressed suicide attempter is most often a white woman who has a history of recent and past stressful events, an unstable childhood and prior medical and psychiatric illness. She is unmarried, has few social supports, and lacks a close friend to confide in. In contrast, the person who completes suicide is most often a white man over 45 who is unemployed, unmarried or widowed, and living alone. He has endured humiliating situations and has a history of medical and psychiatric illness, possibly also of alcohol abuse. These findings parallel those for adolescents and young adults: attempts are made more often by girls who experience high stress and have poor or reduced abilities to handle it, while suicides are completed more by boys who show antisocial behavior and are publicly shamed when being disciplined.

Many clinically depressed people who talk about suicide or attempt it do not succeed in the act. However, recent studies indicate that at least two-thirds of suicide completers do communicate thoughts about killing themselves to family, friends and physicians. Other findings show that a larger number of people who commit suicide are under a doctor's care at the time. It is possible that the seriousness of the depressive condition is often not sufficiently recognized.

Does a tendency toward suicide run in families? That is a possibility that biological and genetic researchers continue to explore. Some adoption studies have shown a raised rate of suicide in the biological relatives of adoptees diagnosed as depressed as compared to their adoptive families or nondepressed control groups. Scientists have also found that compared to nondepressed control groups, clinically depressed people who had attempted suicide and others who had committed suicide have significantly lower levels of the serotonin metabolite 5-HIAA, suggesting that the neurotransmitter itself is low. A decrease in serotonin has long been thought to be associated with clinical depression. Some success has been achieved in predicting the possibility of suicide based on these lowered chemical levels, but the generalizability of the procedure has not been established. Also in question is whether these lowered levels are influenced by genetic predisposition. There may very well be a genetic component to suicide, but exactly how it operates is still unclear.

Suicide prevention is in its infancy. More work needs to be done on all aspects of suicide research: diagnostic, psychological, social, genetic, and biological.

Chapter 5

Treatment Alternatives

Of the estimated 10 to 14 million people in the United States who have a diagnosable depression, only 50 percent actually seek treatment. That means that as this booklet is being read, there are perhaps 7 million clinically depressed people who are not seeking professional help. Why is this?

For those who are rendered barely functional by a major depressive episode, the very severity of the symptoms usually means that help will be sought. But not always. For the elderly, children, and adolescents, the symptoms may not be clear, or may be confused with other conditions. Those who live alone may deteriorate without help. People whose physical illness is accompanied by a clinical depression may not realize that the depression is treatable, and neither may their physicians. For some who are clinically depressed, the symptoms themselves — pessimism, hopelessness, lack of energy — may interfere with help-seeking.

When the symptoms of clinical depression fluctuate or are mild, the picture is even more difficult. In most cases, clinical depression is a remitting disturbance: it lasts an average of about a year. In this country, where "put on a happy face" is a byword, many people just grit their teeth and try to live through a depressive episode. They may think "it's happened before and gone away, maybe it will just go away again this time." And, according to statistics, it probably will. But at what cost does a person push him or herself through a depressive episode, in terms of work, finances, social relationships, and childrearing? Is it worth enduring the lethargy, sleeplessness, and crying spells, hoping that they will "go away"? The question is important because, according to recent statistics, although a clinical depression may "lift," it also may reoccur some time in the future. Researchers now think that more clinical depressions are chronic than had been believed. Unless the depressive pattern is altered in some way, it might have to be borne indefinitely.

Neither the public nor many health professionals are as informed or

knowledgeable about clinical depression as they need to be. One severely depressed man, Russell Hampton, writing in his autobiography, put it this way:

> *If there were a physical disease that manifested itself in some particularly ugly way, such as pustulating sores or a sloughing off of the flesh accompanied by pain of an intense and chronic nature, readily visible to everyone, and if that disease affected fifteen million people in our country, and further, if there were virtually no help or succor for most of these persons, and they were forced to walk among us in their obvious agony, we would rise up as one social body in sympathy and in anger. We would give of our resources, both human and economic, and we would plead and demand that this suffering be eased. There isn't such a physical disease, but there is such a disease of the mind, and about fifteen million people around us are suffering from it. But we have not risen in anger and sympathy, although they are walking among us and crying in their pain and anguish.*

Mr. Hampton is wrong on one count. There *is* help and succor. Effective treatments are available now, despite the enormous amount that still remains to be learned about the causes and manifestations of clinical depression. These treatments will not work for everybody in every circumstance, but they will help a great many people, certainly many who are suffering needlessly in what John Bunyan termed 400 years ago "the slough of despond." Barbara Benziger, a woman who suffered a major depression and went on to write about it, said:

> *It may help someone else to know that with my type of illness, given good care, though you may not believe it during your illness, there is an end to the dark tunnel in which you wander lost and alone for so long. There is an end, and an opening with a light to guide you back to the world you thought you had left forever. There will be detours, landslides, and lost ground, and you may despair, but there is an end and an out.*

Some may see treatment as costly, unavailable, or long and drawn-out. But in fact this is not true. A number of short-term psychotherapies designed to treat clinical depression have been developed in recent years. Antidepressant drugs are widely available and act quickly (in general, signs of improvement are noticeable within 2 to 3 weeks after the initial dosage). Electroconvulsive therapy (ECT) reverses depressive symptoms even more rapidly than drugs. Generally, these treatments are not expensive, especially when the cost is balanced against the loss of productivity and enjoyment that are the concomitants of a clinical depression.

For many people, the question will come down to this: how does anyone know whether a "blue mood" is merely sadness, a transient phenomenon, or a true clinical depression? The best rule of thumb for judgment is assessment of the persistence and severity of the symptoms mentioned earlier in this booklet.

If the "depressed mood" lasts for more than a couple of weeks, and/or if the symptoms, in whatever combination, are causing a noticeable impairment in the person's ordinary mode of functioning, then it is time to think about seeking professional help.

Psychotherapy

Psychotherapies involve the presence of an interested but objective person (the therapist) and the use of talking to define and resolve problems. There are many kinds of psychotherapy, but only a few that are specifically aimed at treating clinical depression. These are short-term treatments whose usual duration is 6 months or less. They include cognitive, behavioral, interpersonal and short-term psychodynamic psychotherapy. Group, marital and family therapies are also possible methods of short-term treatment. All psychotherapies aim at improving personal and social functioning; some are designed to alter thinking processes and others deal more with behavior and interactions with others, although this distinction is somewhat arbitrary and there is obviously much overlap and interconnection. Psychotherapy is useful for some depressed people but not for all. It is clearly not of use if the person is too disabled to talk rationally, is mute, or shows psychotic symptoms. Therefore, it is generally used in mild to moderate depressions.

In the past, research on the efficacy of various forms of psychotherapy yielded little in the way of conclusive findings because of problems with methodology. Diagnoses were not standardized, measures of outcome were often vague or incomplete, and therapists' techniques were often inadequately monitored for consistency. Many of these stumbling blocks have now been removed. A number of short-term therapies for depression have been shown to be effective in controlled studies, although the specific reasons for their effectiveness are not yet known. NIMH is sponsoring investigations in cognitive/behavioral and interpersonal therapy as compared to other types of treatment.

Psychotherapy is also sometimes used in conjunction with drug therapy; many clinicians feel that drugs are useful in dealing with the acute symptoms of clinical depression while psychotherapy is beneficial for long-standing characterological or behavioral problems. Researchers are investigating these suppositions.

Cognitive/Behavioral Therapy

This treatment focuses on the depressed person's negative or distorted thinking patterns. It is characteristic of depressed people to

minimize good events and maximize bad ones, to over-generalize ("if she doesn't love me, nobody will"), and to personalize ("if my child fails at school, I'm a bad mother"). Cognitive therapy assumes that negative thought patterns lead to depressed feelings and behaviors, and that the way to change the feelings is to change the thoughts. The therapist and the depressed person focus on the "here and now" and use both their own interaction and current happenings in the person's life as material for their discussions. The emphasis is on the depressed person's learning to correct distorted thought patterns through various exercises. He or she keeps a daily record of activities and negative thoughts. In treatment sessions, the therapist explains and discusses the examples of distorted thinking, and also uses such tactics as role-playing of distressing situations. The emphasis is on specifically targeted goals, and on developing skills that the person can use after the therapy is ended to continue self-correction and evaluation. The treatment generally requires a maximum of 20 sessions in 10 to 12 weeks.

Behavior Therapies

This group of therapies assumes that depressive behaviors are learned and reinforced in the environment. An example would be the shy, awkward teenage girl who doesn't get asked to dance at a party. She may close in on herself, her shoulders may hunch and her head droop as evidence of this, and her own behavior may discourage would-be dance partners even further. Given enough of this reinforcement, the pattern becomes fixed. Behavior therapy aims at changing not only the individual's behavior but also what is called the "reinforcement field": the environment. There are a number of behavioral therapies available which share a similar orientation; Social Skills therapy will be described as an example.

Social Skills therapy starts by having the depressed person identify specific interactions or situations that are seen as being either pleasant or unpleasant, by means of a self-rated Events Schedule. Therapeutic goals are developed from the schedule; the intent is to modify or change the unpleasant events and increase the pleasant ones. The person monitors him or herself with a daily written activity schedule, and correlates various moods with associated interactions or situations. Other treatment methods include changing the environment, and persuading close associates to praise or pay attention to the depressed person's "positive" behaviors. Specific social skills are taught; self-reward after "good" behavior is encouraged. Other techniques include training the person to stop negative thoughts and to internally dispute irrational ones. The emphasis, as in Cognitive/Behavioral therapy, is on the "here and now," and the goals are identifiable improvements in behavior.

Interpersonal Psychotherapy

This form of therapy deals primarily with disturbances in functioning between the depressed person and others in his or her environment. Depressive symptoms are assumed to arise in the context of grief, uneven relationships ("I love him more than he loves me"), normal life changes and transitions, and the lack of, or unfulfilled, personal relationships. Interpersonal psychotherapy deals with the current life situation and attempts to resolve current problems. To do this, the therapist will teach the depressed person about the nature of clinical depression and they will work together to change the person's immediate environment. The therapist discusses the depressed person's feelings, and deals with the connection between important events and the associated depression (for example, after a divorce, the individual's guilt about real or imagined neglect or lack of communication may be a factor in the depression). The therapist will also discuss and help develop changes in the person's behavior and social skills.

Psychodynamic Psychotherapy

This is currently the most widely used type of psychotherapy. Its underlying theories see depression as a symptom of a complex set of character problems stemming from the person's early childhood experiences with the parents or other close relatives. Psychodynamic psychotherapies aim to treat the "whole person," rather than only the so-called "symptoms," such as depression, that are manifested at any one particular time. However, although most psychodynamic psychotherapy is open ended (no specific duration for treatment is assumed), recently developed short-term variations are being used to treat clinical depressions. These therapies attempt to change or modify the depressed person's usual methods of dealing with others.

A crucial element in psychodynamic psychotherapy is "transference," a situation in which the individual in treatment "transfers" perceptions and feelings about important childhood figures (usually one of the parents) onto the therapist and the therapy sessions. Interpretation of the "transference" phenomenon to the patient is generally done over a long period of time. In the short-term therapies, however, the therapist points out the "transferred perception" to the depressed person fairly quickly, so that the "here and now" relationship can be used immediately to correct behaviors which are carried over from the past. Questioning and confronting about characteristic maladaptive ways of behaving, plus a supportive and understanding attitude by the therapist, are also central to the treatment.

Pharmacotherapy

There are three major types of drugs used to treat affective

disorders: tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs) and lithium. Drugs are generally used for moderate to severe depressions, although in depressions which are immediately life threatening, that is, where the person is actively suicidal or extremely malnourished, ECT is often preferred because of its faster action. There is some indication that tricyclics and MAOIs are effective with some forms of milder depression, often in combination with psychotherapy. Lithium is often used to treat manic episodes and for maintenance treatment of bipolar disorder.

All of these drugs are relatively new; the tricyclics and MAOIs were introduced in the late 1950s, and lithium, although in use earlier in Europe, was not made available in the United States until 1970. Interestingly, each type of drug was discovered by a fortuitous accident. The first tricyclic, imipramine, was uncovered during a search for a more effective antipsychotic agent. The function of MAOIs in alleviating depression was brought to light as a byproduct of research on iproniazid, a drug used to treat tuberculosis. And, although the anti-manic properties of lithium were actually discovered during a search for a treatment for mania, this occurred only because the investigator happened to choose lithium as an aid to his experiments, not because he had any notion that in itself it might be an effective treatment.

The exact way in which these drugs work is not known, although they all alter the action and distribution of brain chemicals. Tricyclic antidepressants are thought to prevent neurotransmitters in the synaptic cleft from being returned to the sending neuron, thus making more of them available for transmitting electrical impulses. The MAOI drugs apparently have a similar effect, achieved, it is thought, by inhibiting the action of MAO, a brain enzyme that destroys neurotransmitters. Lithium's method of action is complex; it seems not only to influence neurotransmitter action, but also to affect electrolytes and other substances and functions of the body. The theorized action of these drugs is described in more detail in the Biology section of chapter 2.

The use of computers and increasingly refined techniques, including noninvasive examination of human subjects, has become more sophisticated over the past 10 years, and scientists' knowledge of brain function is accelerating at a rapid pace. However, the definitive answers are still in the future, and for the present, clinicians and the public continue to use antidepressant drugs because they work. People also use aspirin and find it quite effective, although to date no one has found out exactly why it works either.

Antidepressant drugs tend to act on the somatic symptoms of depression, such as sleeping and eating problems, energy level, and lethargy or hyperactivity. They do not alter characterological behavior patterns, nor do they change the ability to solve life problems, except insofar as, at their most effective, they return the

individual to the level of functioning he or she had before the onset of the depression. As one recovered patient put it: "It isn't that I don't have all the problems I had before — but having problems isn't such a problem."

Before taking any antidepressant medication, it is absolutely necessary to give the treating physician a complete history of all other drugs being taken, including over-the-counter preparations and alcohol in any form. There are two reasons for this: first, some drugs used for physical illnesses create depressions on their own; a person may be suffering from a drug-induced depression and not know it. Many drugs used for hypertension fall in this category. The second reason is that the combination of antidepressants with certain other medications, or with alcohol, can cause bad side effects.

Tricyclic Antidepressants

Tricyclics are the drug of first choice in depression. The most commonly prescribed tricyclics are:

Imipramine HCl (Tofranil, Janimine, Presamine, SK-Pramine)

Amitriptyline HCl (Elavil, Amitid, Endep, Amitril, SK Amitriptyline)

Others include:

Desipramine HCl (Norpramin, Pertofrane)

Doxepin HCl (Sinequan, Adapin)

Nortriptyline HCl (Aventyl HCl, Pamelor)

Protriptyline HCl (Vivactil)

Trimipramine Maleate (Surmontil)

Amoxapine (Asendin)

Tricyclics act in a generally similar fashion overall in relieving somatic depressive symptoms, but differ somewhat in their side effects and in their effect on certain specific somatic symptoms. An individual may tolerate one antidepressant drug well, but not another. Just as there are individual differences in body chemistry, so there are individual responses to drugs. One important difference is the variation in the sedative effect of antidepressants.

While tricyclics vary in their side effects, the most common are dry mouth, constipation, and urinary retention. Since some of these are the same as symptoms of clinical depression itself, if they can be tolerated it is thought worthwhile to bear with them as they generally lessen or disappear as treatment proceeds.

MAOIs

MAOIs are a second-line drug if the tricyclics either do not work or

cannot be tolerated because of the side effects. They appear to be useful for people who overeat and/or oversleep when depressed, as well as for those who also suffer from anxiety and phobias, and are regarded by some clinicians as the drug of choice for these "atypical" depressive conditions.

MAOIs marketed in the United States include:

Isocarboxazid (Marplan)

Phenelzine Sulfate (Nardil)

Tranylcypromine Sulfate (Parnate)

The greatest liability of the MAOIs from the patient's point of view as well as the physician's is the dietary and drug restrictions which must be observed with their use. MAOIs, therefore, can only be used by people who are willing and able to adhere to these restrictions.

The interaction of MAOIs with certain substances in some foods, beverages, and drugs causes a quick and marked rise in blood pressure, which is manifested by a severe and splitting headache and other symptoms. Prohibited foods include such items as processed meats, aged cheeses, and pickles and pickled foods; prohibited beverages include red wines and sherry; drugs include stimulants (such as amphetamines), barbiturates, insulin, and certain cough medicines and nasal decongestants.

MAOIs are generally not recommended for those who are physically ill because of the drugs' interaction with other medications.

Lithium

Lithium is the treatment of choice in the manic phase of bipolar disorder. Because it typically takes from 4 to 10 days for lithium's therapeutic action to occur, in cases of severe mania or hyperactivity an antipsychotic drug may be used initially as well. Lithium is also used as a maintenance drug to prevent or reduce future episodes of bipolar disorder. It is an effective antidepressant for some people but is not the treatment of first choice. It can be used if the person has not responded to tricyclics or MAOIs, and is also used for those who develop manic symptoms after being treated with tricyclics or MAOIs.

Trade names for Lithium Carbonate (the term used in the United States) include:

Eskalith

Lithane

Lithobid

Lithonate

Lithotabs

Regular blood tests are always given during lithium treatment to check the level of the drug. Lithium can be toxic in excessive doses, and there is a narrow range, which varies from person to person, between the therapeutic level and the toxic one.

Initial side effects may include nausea, stomach cramps, thirstiness, muscle weakness, hand tremors, weight gain and feelings of being slightly tired, dazed or sleepy. These effects are usually transient, but some may persist for the duration of the drug treatment.

Other Drugs

There is a good deal of interest in the so-called newer generation of antidepressants. Two drugs recently marketed in the United States, maprotiline HCl (Ludiomil) and trazodone HCl (Desyrel) are being used with increasing frequency because of their purported lower incidence of adverse reactions. In addition, there are two other drugs which will probably be marketed shortly in this country: nomifensine and bupropion. None of these drugs are tricyclics or MAOIs.

Maintenance Treatment

Thus far we have been discussing the use of antidepressant drugs for treatment of the acute, or immediate episode of depression. What about their continued use as preventative agents? There is evidence that antidepressants do have some positive effect as preventative agents when taken on a long term basis. There is still the question whether effective long term maintenance drug therapy prevents the occurrence of new depressive or manic episodes or merely "dampens" emerging recurrences sufficiently to avoid a full-blown episode. Prevailing opinion among researchers is that lithium and the antidepressants may act in either way, depending upon the individual taking the drug. There is general agreement, however, that the "dampening" action may explain more of the drugs' effect than complete prevention of new episodes. The decision to choose maintenance drug therapy is based on the severity and chronicity of the clinical depression, the frequency of episodes, the individual's physical condition, response to the drug's side effects, life situation, and a number of other factors.

Electroconvulsive Treatment

Electroconvulsive treatment (ECT) was first introduced in the 1930's as a general treatment for mental illness. Seizures similar to those occurring in epilepsy were thought to alleviate mental disorders. A number of methods were used to induce these seizures, including chemicals, but since ECT proved superior it gradually became the prevailing treatment and was used extensively until the advent of drug therapy in the mid-1950's.

ECT came into disfavor in the United States in part because early techniques were unrefined, sometimes causing physical injury, and also because it was abused in certain situations. Many of the former problems with the treatment no longer exist; modern methods of administering ECT have made it a relatively simple procedure.

ECT is extremely effective in cases of major depression with somatic symptoms such as sleep and eating disturbances, and particularly in those depressions that are accompanied by psychotic symptoms, for instance, delusions and hallucinations. It is also used to treat people for whom antidepressants have not worked, who cannot tolerate the side effects (especially persons with cardiac problems) or who need an immediately effective treatment because they are acutely suicidal, malnourished, or dehydrated. Elderly patients are often good candidates for ECT when their use of multiple medications makes antidepressant drug therapy problematic.

How does ECT work? Most researchers think that it is the seizures, or convulsions, that have a therapeutic effect and that the electricity is only the mechanism of inducing them. What the seizures actually do to the brain is still unknown. There is speculation that they induce alterations in neuronal transmission similar to those thought to be induced by antidepressant drugs, but results of investigations so far are not conclusive.

Two advantages of ECT are that it is the fastest acting treatment for depression and, in total, it takes the least time of any treatment. Disadvantages include side effects such as memory loss (usually for a short time but sometimes, sporadically, for a long time) and the risks entailed whenever a general anaesthetic is administered.

ECT is in most cases an inpatient procedure. Treatments are usually administered 3 times a week; the total number may vary from 6 to 10, although in some cases more may be required. Improvement is usually apparent after the first 3 or 4 treatments and may be dramatic after the first one. After the last treatment, there is a "convalescent" period of 1 to 3 weeks. The person either remains in the hospital or is discharged in the care of a family member or someone who will look after him or her. This is necessary because of the temporary memory loss that follows the treatments.

ECT is given in a treatment room by a clinical team. The patient is first given an intravenous anaesthetic, and then a muscle relaxant. Oxygen is given, and the electric current is then administered. The entire procedure, from preparation through recovery, usually takes from 20 to 40 minutes.

Side Effects

Complications, although not frequent, may include irregularities of the heartbeat (usually temporary) or, rarely, heart attacks, prolonged seizures, or adverse reactions to the anesthetic or muscle relaxant.

Headache, mild muscle soreness, or nausea sometimes occur, but these usually respond to simple treatment.

The most common side effect is memory loss. Two kinds occur: loss of memory for past events, especially for those events that immediately preceded treatment, and difficulty in retaining newly acquired information after treatment. These memory losses generally disappear a few weeks to a few months after treatment, although in some cases some areas of past memory remain lost. There seems to be evidence that unilateral treatment (administering electric current to only one side of brain) produces less confusion and memory loss than bilateral treatment (administering current to both sides); this is an area of intensive investigation by researchers.

Conclusion

Substantial progress in research in all areas related to the clinical depressive syndromes has been made, and is continuing. Major effort is being concentrated in defining valid subtypes of clinical depression using information from many different areas, including genetics, biochemistry, psychophysiology, documentation of life events, personality, and treatment response and outcome. NIMH continues to support this research and encourages new and promising approaches. The knowledge that has been gained is already being used to prevent the needless suffering caused by clinical depression.

Current NIMH research programs include:

- *The NIMH Clinical Research Branch Collaborative Program on the Psychobiology of Depression*: The overall aim of this 5-year program is to investigate biological and clinical aspects of affective disorders. The Biological Studies section is investigating such areas as neurotransmitters, neuroendocrine and electrolyte systems, and their interrelationships with behavioral systems in depressed persons. The Clinical Studies section addresses the validity of diagnostic systems, genetic hypotheses, and the role of psychosocial factors.

- *The NIMH Collaborative Study of Long Term Maintenance Drug Therapy in Recurrent Affective Illness*: This study is attempting to answer many unresolved questions about drug therapy. Its primary aims are to compare the effectiveness of lithium carbonate, imipramine, placebo, and a combination of lithium plus imipramine in long term maintenance treatment of recurrent major depression and recurrent bipolar disorder.

- *The NIMH Psychosocial Treatment Branch's Psychotherapy of Depression Collaborative Research Program*: This program is comparing five short term treatments for nonhospitalized persons diagnosed as having major depressions. The treatments include Cognitive/Behavioral Therapy; interpersonal psychotherapy; imipramine plus clinical management; pill-placebo plus clinical management; and a "treatment as usual" condition.

In addition to the initiatives described above, the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) and the World Health Organization (WHO) are engaged in a multiyear program on diagnosis and classification of mental disorders, drug abuse, and alcoholism; NIMH is playing a large part in planning and coordinating this effort.

Table 2

FINDING HELP

When to Seek Help:

If you, a relative or friend is experiencing some or all of these symptoms, if they persist for more than two weeks, and/or if they are causing a noticeable impairment in ordinary functioning:

- Sad, depressed, or "empty" mood
- Loss of interest or pleasure in ordinary activities
- Decrease in sexual drive
- Sleep disturbances (insomnia, early-morning waking, oversleeping)
- Eating disturbances (appetite and/or weight loss or gain)
- Decreased energy, fatigue
- Feelings of pessimism, guilt, worthlessness, helplessness, hopelessness
- Thoughts of death or suicide; suicide attempts
- Activity level slows down or increases
- Diminished ability to think and/or concentrate

Where to Seek Help:

A good place to start is your physician's office, or your local health or mental health clinic.
Other possibilities include:

- Community Mental Health Center
- General Hospital department of psychiatry or outpatient psychiatric clinic
- University or medical school-affiliated program
- State Hospital outpatient clinic
- Family service/social agency
- Private clinics or facilities

Referrals to individual practitioners who treat depression may be sought through:

- Family physician
- County Medical Society
- Local chapter of:
  American Psychiatric Association
  American Psychological Association
  National Association of Social Workers